BARRIERS AND ENABLERS TO THE UPTAKE OF DIRECT ORAL ANTICOAGULANTS (DOACS) FOR STROKE PREVENTION IN ATRIAL FIBRILLATION

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Barriers and enablers to the uptake of direct oral anticoagulants (DOACs) for stroke prevention in atrial fibrillation

A qualitative study with patients and staff in three health economies

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Abstract

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Keywords: new medicines, direct oral anticoagulants, DOAC, anticoagulants, uptake, implementation, stroke, atrial fibrillation, diffusion of innovation, shared decision making

Implementation and uptake of novel and cost-effective medicines can improve patient health outcomes and healthcare efficiency. However, the relative uptake of new medicines recommended by the National Institute for Health and Care Excellence often lags behind other comparative countries’ health systems. One example is the uptake of direct oral anticoagulants (DOACs) for stroke prevention in atrial fibrillation, which was slow and had a high level of unexplained variation across different health economies in England. This research aimed to explore barriers and enablers to the uptake of DOACs from the perspectives of patients, healthcare professionals, and key stakeholders by conducting systematic and narrative reviews and semi-structured interviews. Data collected from 21 patients, 23 healthcare professionals, and 23 key stakeholders recruited from three different health economies was analysed using the Framework method. The findings identified a range of intersecting factors acting as barriers and/or enablers to the uptake DOACs. While there were a wide range of experiences and views, an agreement between patients and healthcare professionals/key stakeholders on several identified factors was observed. Attributes of the innovation, characteristics of patients and prescribers, local health economy readiness for change, implementation process, and external health system context were suggested as influences. Mapping of the findings to the Diffusion of Innovations in Service Organisations model identified 11 components for a future toolkit development to facilitate uptake of nationally recommended new medicines. This thesis highlighted the role of patients, consideration of all costs associated with new medicines, and compatibility with the health economy’s care model impact on the uptake.
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Glossary

**Adherence (medicine)** - The extent to which patients take their medicines as prescribed by their clinicians.

**Anticoagulant** - A medicine used to prevent formation of clots in the blood, commonly known as “blood thinners”.

**Anticoagulation** - The process of preventing the clotting of the blood.

**Arrhythmia** - Irregular or abnormal rhythm of the heart.

**Atrial fibrillation** - A medical condition causing an irregular and often abnormally fast heart beat.

**Clinical Commissioning Group** - Clinically-led statutory National Health Service body responsible for the planning and commissioning of local health care services.

**Clinical trial** - A research study comparing the effects of one treatment with another or no treatment.

**Diffusion** - A passive process by which an innovation is communicated over time among the participants in a social system.

**Direct oral anticoagulants** - A group of oral anticoagulants acting directly against certain coagulation factors. Four direct oral anticoagulants are currently available: apixaban, dabigatran, edoxaban, and rivaroxaban.

**General Practitioner** - A community-based medical doctor treating acute and chronic illnesses and providing preventative care and health education to patients.

**Guideline (medicine)** - A document providing guidance on making decisions and criteria for diagnosis, management, and treatment.

**Health economy (local)** - The National Health Service organisations including urgent and emergency care, hospital, community, mental health, and social services involved in the commissioning, development and provision of health services for a local population living within a Primary Care Trust boundary (abolished in April 2013).

**National Institute for Health and Care Excellence** - An executive non-departmental public body, sponsored by the Department of Health and Social Care in the United Kingdom. It promotes clinical excellence in the national health service by developing guidance and recommendations on the effectiveness of treatments and medical procedures.
**New medicine** - New or improved pharmaceutical product which improved people’s health and aimed to add value in the form of improved efficiency, effectiveness, quality, sustainability, safety, and/or affordability.

**Paternalistic decision-making** - A process of medical decision-making where a clinician makes a decision without input from a patient or consideration of a patient’s preferences and wishes.

**Pharmaceutical detailing** - A marketing technique used by pharmaceutical companies to promote and educate clinicians about their product through pharmaceutical representatives meeting directly with clinicians.

**Primary care** - Day-to-day healthcare provided by general practitioners, physician associates, practice nurses, community pharmacists, optometrists, dentists, and NHS walk-in centres.

**Quality Outcome Framework** - A fundamental part of the General Medical Services contract providing remuneration to general practitioners in England for the quality of care provided to their patients.

**Real-world evidence (medicine)** - Evidence on the effects of medicines obtained from clinical practice and outside the context of randomised controlled trials.

**Secondary care** - Planned or unplanned care provided by healthcare professionals who generally do not have the first contact with the patient. “Secondary” often occurs in a hospital setting.

**Shared-decision making** - A collaborative process of medical decision-making when both a clinician and a patient contributes to the decision.

**Stroke** - The sudden death of brain cells due to lack of oxygen, caused by blockage of blood flow or rupture of an artery to the brain.

**Technology appraisal** - Recommendations produced by the National Institute for Health and Care Excellence on the use of new and existing medicines and treatments within the national health service. Recommendations are based on a review of clinical and economic evidence.

**Time in the therapeutic range** - A quality measure used to assess anticoagulation with warfarin. The time in the therapeutic range is calculated by dividing the number of days within the target range by the total number of days in the observation period. The range for patients with AF on warfarin is between two and three.
List of Abbreviations

ABPI - The Association of the British Pharmaceutical Industry

ACC - Accelerated Access Collaborative

AF - Atrial Fibrillation

AHSN - Academic Health Science Network

ARISTOTLE - Apixaban for Reduction In Stroke and Other Thromboembolic Events in atrial fibrillation

BD - Twice a day

CCG - Clinical Commissioning Group

DOAC - Direct Oral Anticoagulant

EMA - European Medicines Agency

ENGAGE AF-TIMI - Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction

ESC – European Society of Cardiology

FDA - Food and Drug Administration

ICER - Incremental Cost-Effectiveness Ratio

INR - International Normalised Ratio

GP - General Practitioner

GPSI - General Practitioner with a Specialist Interest

MHRA - Medicines and Healthcare products Regulatory Agency

NHS - National Health Service

NICE - National Institute for Health and Care Excellence

OD - Once a day

OLS - Office for Life Sciences

PCT – Primary Care Trust

PICOS - Population, Intervention, Comparison, Outcomes, and Study
PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY - Quality-Adjusted Life-Years
QATSDDD - Quality Assessment Tool for Studies with Diverse Designs
QOF - Quality Outcome Framework
RE-LY - Randomised Evaluation of Long-term anticoagulant therapy
ROCKET-AF - Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K for the prevention of stroke and Embolism Trial in Atrial Fibrillation
SAFI – Stroke in Atrial Fibrillation Initiative
SD - Standard deviation
SDM - Shared-Decision Making
SSNAP – Sentinel Stroke National Audit Programme
TTR - Time in Therapeutic Range
UK - United Kingdom of Britain and Northern Ireland
USA - United States of America
WHO - World Health Organisation

**Initials**
BF - Beth Fylan
DP - Duncan Petty
IM - Iuri Marques
JT - Justine Tomlinson
KM - Kristina Medlinskiene
KS - Katherine Stirling
MR - Marcus Rattray
SR - Sue Richardson
Publications and Presentations

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*Health Service Research and Pharmacy Practice Conference 2018*


Medlinskiene K. (2017) Impact of Patient and Public (PPI) on the PhD research study design. [Oral presentation]

**Other thesis related outputs**

*Animated video*

Chapter 1 Introduction

1.1 Introduction

Medicines are the most common therapeutic intervention in healthcare (Ewbank et al. 2018). In the United Kingdom, the relative uptake of new medicines recommended by the National Institute for Health and Care Excellence (NICE) often lags behind other comparative countries’ health systems (OLS 2016). One example is the uptake of direct oral anticoagulants (DOACs) used for stroke prevention in non-valvular atrial fibrillation (AF), which was slow and had a high level of unexplained variation across different health economies (ABPI 2016). There was a risk of inequality of therapy options offered to patients depending on their place of residence. This thesis, therefore, aims to explore the barriers and enablers to the uptake of DOACs from the perspectives of patients, healthcare professionals, and key stakeholders. It also aims to provide recommendations based on the thesis findings to improve the uptake of new cost-effective medicines within local organisations.

This chapter will provide an overview of the new medicines’ journey from discovery to use in clinical practice, approval process, and uptake of new medicines in the UK. The chapter will also describe the use and uptake of DOACs for stroke prevention in AF in England. In addition, factors affecting the uptake of new medicines in the context of implementation science will be described. These discussions will provide context to this thesis and rationale for the aims and objectives stated towards the end of this chapter. Lastly, an overview of the thesis outline will be presented at the end of this chapter.

1.2. New medicines in the UK

1.2.1 Medicine discovery and development process

Whilst every year a number of new medicines are launched, the journey from basic research to use in clinical practice can take over 13 years and requires significant funds (Paul et al. 2010). The medicine discovery and development process comprises of five stages: medicine discovery, pre-clinical testing, clinical development, medicine regulatory agency review, and post-marketing surveillance (ABPI 2012, Paul et al. 2010). Each stage of the process is summarised in Table 1.1. The lengthy, resource intensive, and expensive process unsurprisingly results in highly priced new medicines. The scientific and technological advances could reduce the length of the process and thus cost in the future. Also, as demonstrated by the development of
vaccines for SARS-CoV-2 within a year, the time for the discovery and development process can be significantly reduced with utilising advanced research, having access to funding, government and public support, collaborative working, and fast-tracked regulatory processes (Ball 2021).

**Table 1.1 The medicine development process from discovery to the use in clinical practice (ABPI 2012).**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Time</th>
<th>Average cost</th>
<th>Number of medicinal candidates tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicine discovery</td>
<td>A target is selected (e.g. protein, gene) and a search begins for a molecule or compound that affects the target.</td>
<td>Average 4.5 years</td>
<td>£436 million</td>
<td>5,000–10,000 candidates; each candidate has 0.01% chance of success.</td>
</tr>
<tr>
<td>Pre-clinical testing</td>
<td>The selected potential compounds are tested for indication of safety and efficacy using cells, animals, and computational models.</td>
<td>Average 5.5 years</td>
<td>£97 million</td>
<td>10-20</td>
</tr>
<tr>
<td>Clinical development</td>
<td>This stage consists of three phases of clinical trials in humans: Phase 1- testing in 20 to 100 healthy volunteers; Phase 2- testing in 100 to 500 patients with the targeted disease; Phase 3- testing in 1,000-5,000 patients with the targeted disease to determine safety, efficacy, and overall risk-benefit profile.</td>
<td>Between 6-7 years</td>
<td>£567 million</td>
<td>Phase 1: 5-10 Phase 2: 2-5 Phase 3: 1-2</td>
</tr>
<tr>
<td>Medicine regulatory agency review</td>
<td>Information from all the studies is submitted to the medicine regulatory for review and marketing authorisation.</td>
<td>Range from 6 months to 2 years</td>
<td>£50 million</td>
<td>1</td>
</tr>
<tr>
<td>Post-marketing surveillance</td>
<td>Monitoring of licensed medicine’s safety and efficacy in clinical practice. This stage is also known as Phase 4.</td>
<td>Continuous</td>
<td>N/A</td>
<td>1</td>
</tr>
</tbody>
</table>

However, not all newly marketed medicines become successful as only around 50% of evidence-based interventions become commonly used in practice (Bauer et al. 2015). The time taken to adopt a new medicine by clinicians can vary greatly between medicines, in some cases being as little as one month (Garjon et al. 2012). Only a small proportion of clinicians are early adopters of new medicines as shown by research, indicating that a minority of clinicians do so in the first two years from approval (Anderson et al. 2018; Huskamp et al. 2013). The widespread use of new
medicines occurs, on average, eight years after the launch (Dunn et al. 2012) but this varies greatly between medicines (Dunn et al. 2012; Garjon et al. 2012, Hernandez and Zhang 2017; Huskamp et al. 2013). The slow uptake of cost-effective and novel medicines can delay improvements in patient health outcomes, healthcare efficiency, and even lessen the international competitiveness of the country in the Life Sciences sector (Ewbank et al. 2018; OLS 2016). Hence, reducing the delay between the launch of new medicine and widespread adoption could potentially bring benefits to patients, the healthcare system and in a wider context to the country.

1.2.2 Approval process

Medicines that are granted Medicines and Healthcare products by the Regulatory Agency (MHRA) marketing authorisation are licensed for use in the UK. Before the UK left the European Union, medicines granted the marketing authorisation by the European Medicines Agency (EMA) also had a licence for the use in the UK. Both regulatory agencies consider the safety and efficacy evidence of the new medicine and manufacturing quality in their decision-making. Once the new medicine is launched in the UK its cost-effectiveness and impact are determined by national authorising bodies. In England, the National Institute for Health and Care Excellence (NICE) considers clinical and economic evidence, testimonies from patients, healthcare professionals and commissioners in their decision making. The price of the new medicine could also be negotiated by NICE. In Wales, the process is done by NICE and the All Wales Medicines Strategy Group. In Scotland, it is undertaken by the Scottish Medicines Consortium and in Northern Ireland by the Department of Health. Since 2019, NICE conducts technology appraisals (review of clinical and economic evidence) for all new medicines marketed in the UK. Before 2019, technology appraisals were conducted only for selected new medicines (Collins 2020).

Economic assessment by NICE considers gained quality-adjusted life-years (QALY) and an incremental cost-effectiveness ratio (ICER) for the new medicine. The QALY measures the health benefits of a new medicine by estimating how many years the patient will live due to the new medicine therapy and multiplying each year by the quality-of-life score (0 to 1; 1 being perfect health) (Ogden 2017). For instance, a new medicine providing a perfect health for two years will have two QALYs. The ICER allows the comparison of the total costs of a new medicine to an existing medicine by considering health effects. The ICER is calculated by dividing the difference in total costs by the difference in QUALYs between new and existing medicines (Collins 2020;
Sterne et al. 2017). In other words, it is an indicator for an additional cost per one QALY compared to existing medicine. Although there is no officially stated threshold for ICER to gain the NICE approval, it has been observed that NICE was willing to approve new medicines with maximum ICER threshold between £20,000 and £30,000 per QALY (Collins 2020; Poole 2008; Sterne et al. 2017). Special cases with different ICER thresholds have been reported, for instance, a threshold between £100,000 - £300,000 was reported for new medicines targeting very rare diseases (Collins 2020). A positive funding decision by NICE through their technology appraisal process indicates that the benefits of new medicines were greater than the opportunity cost. The technology appraisal process on average takes 40 weeks for a single new medicine and 60 weeks for a group of medicines (NICE 2021a). However, the average time from the marketing authorisation to NICE recommendation shortened over time. In 2018/2019, it took 8.8 months for NICE to issue a decision, which was 1.2 months quicker than five years previously (OLS 2019).

Since 2005, National Health Service (NHS) clinical commissioners, commissioning services for local communities within clinical commissioning groups (CCG), in England and Wales have had a legal obligation to resource and fund NICE recommended new medicines within three months (or 90 days) of the published decision (Collins 2020, Poole 2008; NICE 2021a). The compliance is self-reported and deemed to be achieved once a patient is able to have a recommended new medicine without local funding or formulary restrictions after a consultation with their clinician (NICE 2021b). Compliance has been reported as an issue in the past (Poole 2008). There is no public national database available assessing the compliance of organisations within local health economies of implementing NICE technology appraisal recommendations. Some NHS Trusts have their compliance reports available with their online medicine formularies. For instance, in the 2018-2019 financial year the reported time to achieve compliance with NICE technology appraisal recommendations took up to 57 days at Manchester University NHS Foundation Trust (2019), up to 97 days at Guy’s and St Thomas’ NHS Foundation Trust (2021), and up to 204 days at Leeds Teaching Hospitals NHS Trust (2021).

Once NICE has recommended a new medicine for use, local organisations automatically add the medicine to their local medicine formularies. At a local level, CCGs are responsible for medicine management within a health economy. They are permitted to adapt medicine management processes to their local area needs (NICE
Thus, CCGs can discuss the place of NICE recommended new medicine in the local clinical pathway in formulary decision-making group meetings. Although recommended new medicines are adopted into local formularies, there have been reports that additional local formulary conditions for some medicine were added. For instance, in some health economies NICE-recommended DOACs were listed as an option after a trial with warfarin (ABPI 2016; Camm et al. 2015; Ho et al. 2020). Thus, it restricted their use and potentially their uptake.

1.2.3 Uptake of new medicines

The relative uptake of NICE-recommended new medicines often lags behind other comparative countries’ health systems (OLS 2019). Comparative countries included Australia, Austria, Belgium, Canada, Finland, France, Germany, Ireland, Italy, Japan, Netherlands, Spain, Switzerland, Sweden, and the United States of America (USA). In the first year, the relative uptake of 86 NICE-recommended new medicines between 2013-2017 was 21% of the average usage seen in the 15 comparison countries. Although uptake increased with every year, it did not reach the average usage of comparison countries five years later. These uptake indicators have hardly changed over the years as seen in Figure 1.1 (OLS 2019).

The issue of slow uptake of cost-effective medicines in the NHS has been recognised by the UK government, which commissioned a review in 2014 on how to accelerate patient access to health innovations, including cost-effective new medicines, within the NHS. In 2016, the review findings were published in the Accelerated Access Report, which proposed a new system to enable rapid adoption of innovations, including NICE-recommended new medicines, both locally and nationally (Taylor 2016). The review acknowledged the need for support, underpinned by incentives and collaboration, to improve local uptake of health innovations and remove barriers to uptake. However, it did not state what these barriers might be, especially at a local level.
As a result of the review, the Accelerated Access Collaborative (AAC) between the NHS, patients, regulators, government, and industry was formed in 2018. The ACC aims to speed up patient access to health innovations bringing benefits to patients and improve health care efficiency by removing barriers. The uptake of NICE-recommended medicines is supported by the ACC through its rapid uptake programme (support for greater and widespread uptake of selected medicines), innovation and technology payment (removing some financial and procurement barriers) and working with Academic Health Science Networks (AHSNs) (NHS England 2021). The ACC report of its 2019/2020 programme states that more than 700,000 patients have been provided access to proven health care innovations and more than £50 million have been saved by the NHS (ACC 2021). This thesis study complements the Accelerated Access Report by producing recommendations for stakeholders to remove local barriers to optimise the uptake of NICE-recommended new medicines.

Fifteen AHSNs were established in 2013 across England to support health economies in speeding up and increasing the uptake of health innovations, including NICE-recommended new medicines. The AHSNs link the NHS with academia, commissioners, and industry, and facilitate health innovation development,
implementation, and commercialisation. One of the national programmes of the AHSN between 2015 and 2020 focused on AF. The aim of the programme was to reduce AF-related strokes (NHS England 2021) by increasing detection of AF in the population through raising public awareness of AF, increasing the use of anticoagulation therapy through supporting clinicians, and maintaining high quality anticoagulation service for patients with AF by supporting patients and clinicians. The programme estimated that over five years 11,734 AF-related strokes were prevented, and 293,348 additional patients were started on anticoagulation therapy, resulting in potential £158 million savings for the NHS (The AHSN Network 2019).

1.3 Atrial fibrillation and anticoagulation

1.3.1 Atrial fibrillation

AF is the most frequently encountered cardiac arrhythmia, also known as an irregular pulse, affecting over 33 million people worldwide (Chugh et al. 2010; Lippi et al. 2021). Patients with AF may experience palpitations, chest discomfort, breathlessness, tiredness, or dizziness (NICE 2020a). However, up to 40% people, more likely male, will have asymptomatic AF (Xiong et al. 2015).

Globally the prevalence of AF has been rising (Lippi et al. 2021). AF prevalence is higher in men with the male/female ratio of 1.11 (Lippi et al. 2021). In the UK, the prevalence of AF increased from 1.71% in 2015/16 to 2.05% in 2019/20 (NHS Digital 2020). The incidence of AF increases with advancing age and one in five people aged 55 years or older will develop AF in their lifetime. The risk increases to one in three, if at least one risk factor is present such as smoking, alcohol misuse, obesity, hypertension, diabetes, heart failure, and history of myocardial infarction (Staerk et al. 2018). The increase in the observed prevalence could be attributed to the ageing population and increasing incidence of cardiovascular disease (Steinberg et al. 2017), and efforts of national campaigns to increase awareness of AF leading to better detection of people with AF (AF Association 2021; The AHSN Network 2019).

Importantly, the main complication of AF is stroke and thromboembolism (NICE 2014a). Stroke is one of the leading causes of death and disability in England with annual £8.6 health and social care costs in the UK (Patel et al. 2020). AF accounts for approximately one third of ischaemic strokes (Friberg et al. 2014) as patients with AF are at a five-fold increased risk of developing stroke (NICE 2014b), regardless of experiencing symptoms or not (Xiong et al. 2015). Moreover, ischaemic strokes
associated with AF, which are preventable, were shown to possess higher mortality and greater disability rates compared to non-AF related strokes (Lamassa et al. 2001). AF increases cardiovascular mortality and morbidity, and costs to the health care systems (Cowan et al. 2018, Kirchhof et al. 2016). Thus, stroke prevention in AF is a major priority in managing patients with AF.

1.3.2 AF-related stroke prevention

In the UK, it was estimated that 25,000 patients had undiagnosed AF and better diagnosis and optimal use of oral anticoagulants could prevent 7,000 AF-related strokes and 2,000 premature deaths every year (NICE 2014a). The risk of AF-related strokes can be reduced with optimal use of anticoagulation therapy (NICE 2014b; Cowan et al. 2018), with oral anticoagulants, being favoured. Unless the patient receives a successful medical procedure or intervention to return the patient’s heart to sinus rhythm (e.g. catheter ablation, cardioversion, or pacemaker), anticoagulation in AF is a long-term indication (NICE 2014b).

The risk of stroke is determined by calculating CHA$_2$DS$_2$-VASc stroke risk score (Table 1.1). The higher the score, the higher the annual risk of developing AF-related stroke without anticoagulation therapy (Lip et al. 2010). For instance, a risk score of 1 has less than 1% and a risk score of 5 has 10% annual risk of stroke, transient ischaemic attack, or systemic embolism (Friberg et al. 2012). The CHA$_2$DS$_2$-VASc replaced CHADS$_2$ stroke risk score in NICE AF management guideline in 2014. The CHADS$_2$ score had similar characteristics to CHA$_2$DS$_2$-VASc score by considering congestive heart failure history, hypertension, age (≥75 years), diabetes mellitus history, and prior stroke or transient ischaemic attack (Friberg et al. 2012). However, the CHA$_2$DS$_2$-VASc score provides a more comprehensive stroke risk assessment and identifies patients with AF who are at a very low risk of stroke (Friberg et al. 2012).

The current NICE AF management guideline recommends that anticoagulation therapy should be considered in male patients with a CHA$_2$DS$_2$-VASc score of 1 and offered to all patients with a score of 2 or higher (NICE 2014b). This NICE recommendation is unlikely to change in the expected update of the guideline in 2021 (NICE 2020d). Aspirin was also removed from recommendations as therapy for stroke prevention due to it being less effective than oral anticoagulants (Hart et al. 2007; ESC 2016; NICE 2014b). Overall, the changes in national and international guidelines recommendations in stroke risk calculation (move from CHADS$_2$ to CHA$_2$DS$_2$-VASc) and removal of the
recommendation of antiplatelet therapy supported the greater use of oral anticoagulants.

**Table 1.2 Risk factors considered when calculating CHA\textsubscript{2}DS\textsubscript{2}-VASc stroke risk score (adapted from Lip et al. 2010).**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65-74 years old 1</td>
</tr>
<tr>
<td></td>
<td>≥75 years old 2</td>
</tr>
<tr>
<td>Female sex</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure history</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension history (including treated hypertension)</td>
<td>1</td>
</tr>
<tr>
<td>Prior stroke or transient ischaemic attack or systemic embolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease history</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus history</td>
<td>1</td>
</tr>
</tbody>
</table>

Oral anticoagulant therapy choices for patients with AF have expanded in the last decade. Vitamin K antagonists, predominantly warfarin, were the oral anticoagulants of choice before the introduction of four DOACs in the last decade (Bai et al. 2019; Kirchhof et al. 2016). Warfarin therapy decreases the relative risk of AF-related stroke compared to placebo by 64% (Hart et al. 2007) provided optimal levels of anticoagulation are achieved. Due to the pharmacokinetic properties of warfarin, that lead to individual differences, warfarin requires regular international normalisation range (INR) monitoring, which indicates how long it takes for the blood to clot. Warfarin also has numerous food and drug interactions, and patient characteristics and comorbidities can result in labile INR readings. The target INR is usually 2.5, with a range of two and three. Time in therapeutic range (TTR) below 65% indicates poor anticoagulation control with warfarin (NICE 2014b). Patients with TTR<65% were observed to have an increased risk of AF-related stroke (2.6-fold), major bleeding (1.5-fold), and all-cause mortality (2.4-fold) (Haas et al. 2016). A longitudinal study of over 140,000 AF patients in the UK over 12 months concluded that only 44% of patients on warfarin had TTR>70%. Also, 14% of patients had TTR<40%, which is thought to offer no more stroke protection than no warfarin at all (Macedo et al. 2015). Thus, achieving good anticoagulation control with warfarin is challenging in real practice.

All four DOACs are available in the UK and have received positive NICE technology appraisal recommendations: dabigatran in March 2012, rivaroxaban in May 2012, apixaban in February 2013, edoxaban in September 2015. The efficacy and safety of DOACs for stroke prevention in AF has been demonstrated in landmark clinical trials:
dabigatran in RE-LY (Connolly et al. 2009), rivaroxaban in ROCKET AF (Patel et al. 2011), apixaban in ARISTOTLE (Lopes et al. 2010), and edoxaban in ENGAGE AF-TIMI (Giugliano et al. 2013). In randomised clinical trials, DOACs were shown to be non-inferior to warfarin in reducing the risk of AF-related stroke and systemic embolism and only dabigatran (150mg BD) and apixaban (5mg BD) were demonstrated to be more effective than warfarin (Connolly et al. 2009; Giugliano et al. 2013; Lopes et al. 2010; Patel et al. 2011). Also, only dabigatran (150mg BD) significantly reduced ischaemic stroke compared to warfarin (Connolly et al. 2009). A network meta-analysis study of randomised controlled trial data and post-trial real-world evidence studies concluded that DOACs were associated with lower all-cause mortality (Lopez-Lopez et al. 2017). Looking at specific DOACs in network meta-analysis studies: apixaban (5mg BD), dabigatran (150mg BD), edoxaban (60mg OD), and rivaroxaban (20mg OD) were suggested to be more effective in reducing AF-related stroke than warfarin, dabigatran (150mg BD) had lower ischaemic stroke risk, and rivaroxaban (20mg OD) had greater myocardial infarction risk reduction compared to warfarin (Lopez-Lopez et al. 2017; Sterne et al. 2017). Also, network meta-analysis studies concluded that DOACs had lower rates of intracranial bleeding than warfarin (Lopez-Lopez et al. 2017; Ntaios et al. 2017; Ruff et al. 2014; Sterne et al. 2017). Major bleeding risk was lower with apixaban (5mg BD), dabigatran (110mg or 150mg BD) and edoxaban (30mg or 60mg OD) compared to warfarin (Lopez-Lopez et al. 2017; Sterne et al. 2017). Gastrointestinal bleeding risk was lower with apixaban (5mg BD) and edoxaban (30mg OD) compared to warfarin; and clinically relevant non-major bleeding was lower with apixaban (5mg BD) and edoxaban (30mg or 60mg OD) compared to warfarin (Lopez-Lopez et al. 2017). Rivaroxaban, dabigatran (110mg or 150mg BD), and edoxaban (60mg OD) had higher gastrointestinal bleeding rates than warfarin (Lopez-Lopez et al. 2017; Ntaios et al. 2017), and dabigatran (150mg OD) had higher rates of clinically relevant bleeding (Lopez-Lopez et al. 2017) compared to warfarin. Differently to warfarin, which is reversible with vitamin K, DOACs at the time of their introduction had no reversal agent. The importance of a reversal agent for DOACs is debatable since DOACs have much shorter half-lives compared to warfarin. Now there are specific reversal agents available for dabigatran (agent-idarucizumab; since 2015), rivaroxaban and apixaban (agent-andexanet alfa; since 2019 but not yet approved by NICE).
DOAC therapies reduce the need for regular coagulation monitoring, have simpler dosing regimens, and fewer known drug or food interactions (Bai et al. 2019; Kirchhof et al. 2016; NICE 2014b; Orlowski et al. 2021) and have therefore led to a decrease of warfarin and increase of DOAC use in patients with AF over the years (Loo et al. 2017). Although DOACs offer advantages over warfarin, their limitations compared to warfarin include contraindication in patients with valvular heart disease and severe renal impairment.

The optimal use of oral anticoagulants in patients with AF was predicted to save the NHS £241m, across England over three years (NICE 2014a). However, the use of oral anticoagulants is not yet optimised for AF patients despite highly effective anticoagulation therapies available for AF and the impact of AF-related stroke on patients and the healthcare systems. The latest data from the national audit programme in the UK (Figure 1.2) suggest that only 64% of patients with AF admitted to hospital with stroke were taking an oral anticoagulant, 9% were taking ineffective antiplatelet therapy and 27% were not receiving any therapy. The data highlight that, due to sub-optimal use of oral anticoagulants in AF patients, the risks to people developing AF-related stroke requires improvement.
Anticoagulation of patients with known AF on admission for stroke in England, Wales and Northern Ireland between 2013 and 2020 (King’s College of London 2020). The average number of cases per year was 16,427 patients.

1.3.3 Uptake of DOACs in England

Although DOACs were nationally recommended, shown to be effective and safe, and offered advantages over warfarin, their uptake in England has been slower than expected. It was anticipated that the DOAC uptake would be 20% of all oral anticoagulant prescribing in early 2014, a year after publishing dabigatran, rivaroxaban, and apixaban NICE technology appraisals. Also, NICE estimated that 35% of patients with AF requiring anticoagulation will receive DOACs due to the changes to NICE AF management guideline in 2014 (recommending DOACs and removing aspirin) (NICE 2014b). However, in mid-2015, the average uptake of DOACs of all oral anticoagulants in England was 16.5% (ABPI 2016). In less than a third (27%) of CCGs DOACs prescribing was at or above 20% of all oral anticoagulants and in few CCGs (3%) it was at or above 35% (ABPI 2016).

Not only has the uptake of DOACs been slow, but there is also a high level of unexplained variation across CCGs, where DOACs ranged from 4% to 70% of all oral anticoagulant prescribing after a year they were recommended by NICE (ABPI 2012)
(Figure 1.3). The observed variability was also echoed during the patient and public involvement consultation at the design stage of this thesis study (detailed description in Chapter 4) that suggested the possibility of inequality of therapy options offered to patients depending on their place of residence.

Although DOAC uptake was initially slow and variable it has substantially increased over the years in the UK (Cowan et al. 2018; Loo et al. 2017; Medlinskiene et al. 2019; Orlowski et al. 2021). In England, during the period 2011-2014, 95% of patients were prescribed warfarin and 5% DOACs, whereas during the period 2014-2017, 59% of patients were prescribed warfarin and 41% DOACs (Orlowski et al. 2021). Although the number of patients receiving DOACs increased substantially over the years, the overall prevalence of warfarin prescriptions was higher than DOACs (Orlowski et al. 2021). Thus, suggesting that many patients might not be provided with the option of either starting on or switching to DOAC therapy, which could have less impact on their daily lives. Despite the incomplete uptake of DOACs, the increased use of DOACs has been demonstrated to have a positive impact on reducing AF-related strokes without increasing the risk of intracranial bleeding (Orlowski et al. 2021).

The uptake of DOACs was also varied in the studied health economies in this thesis, which is described in detail in Chapter 4.
1.4 Implementation science

1.4.1 Theoretical approaches

In the last two decades, implementation science has gained momentum in health care research as translating research findings into routine practice gained more importance (Bauer et al. 2015). Implementation science is defined as a “scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice, and, hence, to improve the quality and effectiveness of health services and care.” (Eccles and Mittman 2006). Currently, there is a considerable amount of scientific literature exploring why the implementation of evidence-based interventions succeeds or fails within a complex healthcare environment (Nilsen 2015). Nilsen (2015) identified five types of theoretical approaches used in implementation science: process models, determinant
frameworks, classic theories, implementation theories, and evaluation frameworks (Figure 1.4).

**Figure 1.4 Theoretical approaches used in implementation science (Nilsen 2015). Reprinted from Nilsen (2015) under Creative Commons Attribution License.**

Classic theories (or classic change) are classed as theories developed outside the implementation science field such as psychology or sociology. These theories provide a description of the change mechanism and an explanation of how the change occurs. Whereas implementation theories (e.g., COM-B by Michie et al. (2011)) were developed or adapted specifically to understand and explain the implementation of innovations (Nilsen 2015).

The most recognised classic theory explaining the diffusion of innovations is the Diffusion of Innovations theory by Rogers (1962). Diffusion has been defined as "the process by which an innovation is communicated through certain channels over time among the members of a social system" (Rogers 1962, p.10). The theory states that four main elements influence the process:

1. Innovation - a new practice, idea, or object with perceived attributes of relative advantage, compatibility, complexity, trialability, and observability, as well as its potential for reinvention.
2. Communication channels - the ways the information about the innovation is communicated to potential adopters, e.g. mass media, interpersonal channels.
3. Time - concerned with time from learning about the innovation to its adoption or rejection. Five adopter categories were identified: innovators, early adopters, early majority, late majority, and laggards.

4. Social system - "a set of interrelated units that are engaged in joint problem solving to accomplish a common goal" (Rogers 1962, p.24). Aspects of the social system influencing the diffusion are the social structure, system norms, opinion leaders and change agents.

The theory also highlights the role of intermediary actors (opinion leaders, change agents and gate-keepers) in achieving successful adoption and implementation (Rogers 1962). The Diffusion of Innovations theory had a significant influence on the development of implementation determinant frameworks. Determinant frameworks suggest determinants that act as barriers or enablers to the uptake of innovation.

One of the most recognised, cited, and used determinant frameworks that built on Rogers' theory is the Diffusion of Innovations in Service Organisations model by Greenhalgh et al. (2004). The model was developed from a comprehensive systematic review of published empirical studies from 13 different research areas that explored the diffusion of health service innovations (Greenhalgh et al. 2004). Greenhalgh's et al. (2004) model focused on the diffusion of innovations in a healthcare setting aiming to "improve health outcomes, administrative efficiency, cost-effectiveness, or users' experience and that are implemented by planned and coordinated actions" (p.582).

The model proposes nine interacting elements influencing the diffusion of innovations: the innovation, adoption by individuals, assimilation by the system, communication and influence, system antecedents for innovation, system readiness for innovation, the outer context (inter-organisational networks and collaboration), implementation process, and linkage among components of the model. Other commonly used determinant frameworks in healthcare research include Consolidated Framework for Implementation Research or CFIR (Damschroder et al. 2009), or Theoretical Domains Framework (Cane et al. 2012).

Although the frameworks differ in the terminology used, there is considerable overlap between them (Nilsen 2015). The main determinants addressed in these frameworks concern characteristics of innovation; adopter; end-user; context; and strategy to facilitate implementation (Nilsen 2015). Although the outcomes of the frameworks were not specific to successful implementation of new medicines, exploring the main determinants could potentially identify factors affecting uptake of new medicines. The
main broad determinants in the context of new medicine uptake would be characteristics of new medicine (innovation), clinicians and organisation (adopter), patients (end-users), and implementation process (strategy).

1.4.1 Barriers to new medicine uptake

Three previous reviews have explored factors influencing the uptake of new medicines. Mason (2008) and Chauhan and Mason (2008) focused on new medicine use by primary or secondary care prescribers, respectively, and with a primary interest in studies conducted in the United Kingdom (UK). The third review was a systematic review by Lubloy (2014) of quantitative studies from both primary and secondary care. The impact of characteristics of innovation, i.e., new medicine, such as effectiveness, safety profile, convenience, and therapeutic novelty of new medicines were considered as important. Reviews concluded that cost was of low importance (Chauhan and Mason 2008; Mason 2008; Lubloy 2014), but cost could be a factor in current healthcare systems as balancing increasing expenditure on medicines and available funding is becoming harder (Ewbank et al. 2018). The prescribers’ (adopter) scientific orientation, experience, knowledge, and prescribing habits were suggested to influence the uptake (Chauhan and Mason 2008; Mason 2008; Lubloy 2014). The impact of an organisation’s (adopter) characteristics, e.g. size, ownership, was suggested to have limited impact (Mason 2008; Lubloy 2014). At the end-user or patient level, earlier reviews indicated patients’ socio-demographic and economic characteristics influenced the uptake of new medicines. However, patients’ influence through their involvement in decision-making was relatively unexplored. Also, other factors such as peer influence, pharmaceutical detailing, scientific literature and meetings, and regulatory pressures were identified as potential factors affecting the uptake (Chauhan and Mason 2008; Mason 2008; Lubloy 2014).

Although these earlier reviews provided some insight into the determinants of new medicine uptake, the methodological approaches had limitations (e.g. single author, narrative review, narrow search, no quality assessment of reviewed evidence). Also, healthcare systems have changed significantly over the last ten years with an increasing focus on patient-centred care and patient involvement in decision-making (Loughlin et al. 2019), use of medicines (Ewbank et al. 2018), expenditure on medicines (Ewbank et al. 2018), and new policies being developed to improve patient access to new medicines (Department of Health 2008). Studies in earlier reviews might
not have captured all factors relevant to current healthcare systems and further exploration is needed.

1.5 Aims and objectives

The overall aim of this research was to identify barriers and enablers to the uptake of DOACs in three different health economies in North England, United Kingdom.

The translational aim of the project was to produce recommendations to optimise local implementation of NICE-recommended new medicines for long-term conditions.

The objectives were:

- To examine the existing evidence of barriers and enablers to the uptake new of medicines.
- To examine the existing evidence on patients with AF involvement in decision-making on oral anticoagulant therapy and their influence on the uptake of DOACs.
- To understand the implementation process of new medicines within the studied health economies.
- To explore perceptions of patients with AF on the barriers and enablers to the uptake of DOACs.
- To explore perceptions of key stakeholders and healthcare professionals on barriers and enablers to the uptake of DOACs.
- To produce recommendations based on the study findings to improve the uptake of NICE-recommended new medicines.

1.6 Thesis outline

This thesis consists of eight chapters and each is briefly described below:

Chapter 1 - Background

This chapter has provided the background to the thesis and rationale for the study undertaken. It comprises of evidence demonstrating the proposed factors affecting the implementation of health innovations, the issue of the uptake of NICE-recommended new medicines in England, clinical importance of DOACs, and why the uptake of DOACs was highlighted as an issue.

Chapter 2 - A systematic review of barriers and enablers to the uptake of new medicines into practice at organisation level
The systematic review with a narrative synthesis of findings summarises the existing evidence on reported factors influencing the uptake of new medicines. The review also indicates that a better understanding of factors, especially patient, prescriber, and organisational, affecting the uptake of new medicines into clinical practice was needed. The findings of the systematic review are discussed in the context of existing literature to inform the development of research questions and design of the research study described in this thesis. The findings are discussed in more detail in the overall discussion (Chapter 8).

Chapter 3 - Narrative literature review of patients’ involvement in decision-making about oral anticoagulants for stroke prevention in non-valvular AF

The systematised narrative review explores patient role in the uptake of DOACs through their involvement in decision-making. The findings indicate that patient involvement in decision-making was limited and reported by studies when warfarin with at least one DOAC were available. The review also highlights that evidence of patient influence on decision-making was sparse and further research was needed. The findings of the review are discussed in the context of existing literature to inform the development of research questions and design of the research study described in this thesis. The findings are discussed in more detail in the overall discussion (Chapter 8).

Chapter 4 - Methodology

The fourth chapter offers the rationale for the research methods used and describes how the study was conducted. It also describes the local health economies studied in this thesis.

Chapter 5 - Factors affecting the uptake of new medicines: perspectives of patients

The fifth chapter presents the findings of a qualitative analysis of semi-structured interviews with patients. The results suggest the barriers and enablers identified by patients to the uptake of DOACs for stroke prevention in AF and their involvement in the decision-making. The findings are discussed in detail in the overall discussion (Chapter 8).

Chapter 6 - Factors affecting the uptake of new medicines: perspectives of healthcare professionals and key stakeholders

The sixth chapter presents the findings of a qualitative analysis of semi-structured interviews with healthcare professionals and key stakeholders. The results suggest the
barriers and enablers identified by healthcare professionals and key stakeholders to the uptake of DOACs for stroke prevention in AF. The findings are discussed in detail in the overall discussion (Chapter 8).

Chapter 7 - Proposal of toolkit components to facilitate the uptake of new medicines in clinical practice

In the seventh chapter, the thesis findings were mapped to the Diffusion of Innovations in Service Organisations model to produce the potential components of a toolkit for use in clinical practice to address the identified barriers to the uptake of new medicines.

Chapter 8 - Discussion and Conclusions

The final chapter discusses the key findings of the thesis from qualitative interviews in the context of wider literature and draws on systematic and narrative literature review findings to broaden the current knowledge on the barriers and enablers to the uptake of new medicines. This chapter also describes the strengths and limitations of the undertaken work, highlights implications for practice and policy, and proposes recommendations for future research.
Chapter 2 Barriers and facilitators to the uptake of new medicines into clinical practice: a systematic review

2.1 Introduction

As described in the previous chapter, in the UK the relative uptake of NICE-recommended new medicines often lags behind other comparative countries' health systems (OLS 2019). Earlier reviews (Chauhan and Mason 2008; Mason 2008; Lubloy 2014) provided insight into determinants for new medicine uptake (such as medicine, prescriber, patient, organisation, and external environment factors), but the methodological approaches used had limitations (for example, single author, narrative review, narrow search and no quality assessment of reviewed evidence). Also, healthcare systems have changed over the last ten years, thus studies in earlier reviews might not have captured all factors relevant to current healthcare systems and hence an updated review is warranted.

This review, therefore, aims to identify barriers and facilitators affecting the uptake of new medicines into clinical practice, including areas for future research. Also, the review sought to provide more insight on the factors unexplored in earlier reviews such as patient influence and cost of new medicines.

2.2 Method

A protocol for the systematic review was developed and published on the PROSPERO register for systematic reviews (registration number: CRD42018108536). The Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines were followed (Moher et al. 2009). At least two reviewers were involved in each stage of the systematic review (selection of studies, quality assessment, synthesis of results).

2.2.1 Eligibility criteria

The inclusion criteria were established using the PICOS framework (population, interventions, comparators, outcomes, and study design) (Liberati et al. 2009). Four elements of the PICOS framework were relevant to this systematic review (population, intervention, outcomes, and study design). Each selection criterion with rationale are outlined below:

Inclusion criteria:
• Types of study: No restrictions to types of study were made to gain a better understanding of the subject; thus qualitative, quantitative or mixed-methods empirical studies were eligible.

• Population: Studies with adult participants (18 years and older) requiring or taking any new medicine(s) for any condition were eligible. The World Health Organization (WHO) definition of health innovation was used to define “new medicine” as a new or improved pharmaceutical product that improved people’s health and aimed to “add value in the form of improved efficiency, effectiveness, quality, sustainability, safety and/or affordability” (WHO 2020).

• Intervention: Studies were conducted in the context of healthcare organisations in primary or secondary care setting, e.g. hospitals, general practitioner practices.

• Outcome: Identified factors affecting (impeding or facilitating) the uptake of new medicines. Uptake was considered as the use of a new medicine within a healthcare organisation within five years after it had been approved by the regulatory agency of the country where the study was conducted.

• Publication and language: The search covered a ten-year publication period (2008-2018) in order to capture studies relevant studies to current healthcare systems. Only studies published in English were included due to financial and time constraints related to translation.

Exclusion criteria:

• Types of study: Grey literature (conference proceedings, posters, opinion pieces, Theses), review articles, clinical guidelines, and incomplete studies.

• Population: Studies looking at paediatric populations; Established medicines use (adopted for longer than five years).

• Outcome: Studies that only reported prescribing trends and/or patient demographics (age, gender) and clinical comorbidities were excluded.

2.2.2 Search terms and information sources

The search strategy was designed in collaboration with a subject librarian. The search was conducted in seven electronic databases: Medline, EMBASE, Web of Science, CINAHL, Cochrane Library, SCOPUS, and PsychINFO. The search terms were combined with Boolean operators (AND/OR) and truncation symbols for variant word endings and spelling were used. The search terms were developed from four search categories: “uptake”, “new medicine”, “healthcare organisation”, and “barriers and
facilitators”. The search terms were adapted to match keywords used in specific electronic databases. The full search strategy for the MEDLINE database is shown in Appendix A. Additionally, hand-searching was conducted using Google Scholar, reference lists, and forward citations of included studies and relevant systematic reviews to supplement database searches.

The search was completed on 4 September 2018 and updated on 23 April 2020. Reference management software (EndNote X7®) was used to organise and manage the search results. The searches were conducted by one reviewer (thesis author, KM)

2.2.3 Selection of studies

After the removal of duplicates using the reference management software (EndNote X7®), one reviewer (KM) independently screened titles and abstracts using the inclusion and exclusion criteria. The second reviewer independently screened 20% of rejected articles to minimise the removal of potentially relevant studies (Shamseer et al. 2015). Two reviewers independently reviewed full-texts of potentially relevant studies. The first reviewer screened the reference lists and forward citations, and the second reviewer independently reviewed studies deemed to meet the eligibility criteria. Any disagreements were discussed to reach a consensus. If consensus was not reached, the third reviewer reviewed disagreements.

2.2.4 Data extraction

A developed data extraction tool (Centre for Reviews and Dissemination 2009) was piloted with five studies before being finalised. All included studies were read in depth and abstracted information included:

- Author(s), publication year and country of publication.
- Aim(s) and/or objective(s) relevant to this systematic review.
- Study design.
- Data source.
- Setting of the study.
- New medicine(s) studied.
- Sample information.
- Key findings relevant to this systematic review.
- Funding source and reported conflict of interest.
2.2.5 Quality assessment

Two independent reviewers appraised the methodological quality of included studies by using the Quality Assessment Tool for Studies with Diverse Designs (QATSDDD). The QATSDDD tool has been selected as it is designed for quality assessment of studies with diverse research design. It evaluates both qualitative and quantitative aspects of the study (Sirriyeh et al. 2012). The QATSDDD tool consists of 16 criteria (14 criteria for quantitative, 14 criteria qualitative, and six criteria for mixed-methods studies). The tool has been validated and used previously in systematic reviews (Hoorn et al. 2016; Lamore et al. 2017).

The following aspects of studies were examined: theoretical framework; aims and objectives; research setting; sample size and representativeness; data collection procedure and rationale; recruitment; appropriateness, reliability and validity of data analysis tools or process; user involvement; strengths and limitations. Reviewers scored each study on a scale of 0 (not at all/not stated) to 3 (complete/explicitly stated) against the criterion. The maximum score of 42 was for quantitative and qualitative studies and 46 for mixed-methods studies. Disagreements were resolved through discussion or by a third reviewer (KM, JT, or IM).

After assessment mean scores, expressed as a percentage (0-100%), were calculated. Studies were categorised as being of low (<50%), moderate (50% to <70.0%), or high (>70.0%) quality. Although the low methodological quality studies were not excluded, they were given less weight in the synthesis of results and conclusions.

Test-retest (inter-rater) reliability was calculated for studies assessed by the two reviewers. It was evaluated by calculating Interclass Correlation Coefficients (ICCs) estimates and their 95% confidence intervals with SPSS® 24 on a single measures, 2-two-way mixed effect, absolute agreement model. ICCs scores of less than 0.5 were classed as poor, 0.5 to 0.75 moderate, 0.75 to 0.9 good and 0.9 to 1 excellent (Koo and Mae 2016).

2.2.6 Synthesis of results

A narrative synthesis using the Framework method (Ritchie and Spencer 1994), specifically, a “best fit” framework method (Carroll et al. 2011) was conducted to summarise the findings of reviewed studies. The findings of included studies were coded and organised using preliminary categories. The preliminary categories were
based on a multi-level framework by Chaudoir et al. (2014). The framework was developed by collecting implementation success factors for health innovations from multiple previous frameworks. The categories were patient, provider, innovation, structural, and organisational. New categories were generated for data that could not be coded against the framework. The reviewing and summarising of the coded data were completed using NVivo11 software to create matrixes. Then, each matrix was individually cross-examined to identify factors affecting the uptake of new medicines. Finally, these factors were grouped to develop themes and subthemes.

Two reviewers (KM and IM) independently coded the material, and any discrepancies were resolved through discussion. Identified factors and thematic areas were finalised in a team discussion (KM, DP, SR, KS).

2.3 Results

2.3.1 Study selection

The study selection process is summarised in the PRISMA flow-diagram in Figure 2.1. The search yielded 63,064 potential articles and after the removal of duplicates, this was reduced to 43,697 unique titles. Screening of titles and abstracts resulted into 186 studies for further screening and after a full-text review, 138 papers were excluded. Reasons for exclusion were no barriers/facilitators identified (n=51), not a new medicine(s) (n=50), only patient demographics described (n=17), no focus on the uptake (n=11), prescribing trend at a country level (n=6), and a full-text was unavailable (n=3) through the University of Bradford Library Service or NHS Evidence. Eighteen additional studies were included after the screening of reference and forward citations of included studies. A total of 66 studies reporting barriers and/or facilitators to the uptake of new medicines within healthcare organisations were included in the systematic review.

Out of 66 included studies, 11 studies were included in the Lubloy (2014) review and six studies included in this review could have potentially met the eligibility criteria for the Lubloy review (2014). No studies from Mason (2008) and Chauhan and Mason (2008) reviews were included as their reviewed studies were published before 2008.
Figure 2.1 PRISMA flow diagram showing the systematic literature search and screening process.

2.3.2 Study characteristics

Characteristics of included studies, published between 2008 and 2020, are summarised in Table 2.1. Thirty-four studies were conducted in the USA, six in Taiwan, four in Canada, two in Australia, Germany, Ireland, Spain, Sweden, UK, and one in Belgium, China, Czech Republic, Denmark, France, Greece, Hungary, Japan, Thailand, and Balkan countries. Most of the studies (n=62) used quantitative methods; three were qualitative, and one used mixed-methods. The predominant source of data collection was secondary data (n=48) from various databases and registries, e.g. prescribing, insurance, or pharmacy claim databases. Other studies (n=18) used online or printed surveys, semi-structured face-to-face or brief telephone interviews,
patients’ medical records, prescriptions from community pharmacies, or a focus group to collect primary data. Studied new medicines were from 20 different therapeutic classes and five studies described medicines as newly marketed. Medicines explored in reviewed studies were oral anticoagulants (n=14), antidiabetic (n=10), antihypertensives (n=8), cyclooxygenase-2 inhibitors (n=7), medicines for alcohol and substance misuse (n=6), oral chemotherapy (n=5), antidepressants (n=5), antipsychotics (n=4), biologics (3), antiepileptics (n=3), statins (n=2), antiretroviral (n=2), antihistamines (n=2), nonsteroidal anti-inflammatory drugs (n=2), antibiotic (n=1), antimuscarinic bronchodilator (n=1), antiplatelets (n=1), bisphosphonates (n=1), erythropoiesis-stimulating agents (n=1), fibrinolytics (n=1), proton-pump inhibitors (n=1), sex hormones (n=1), and thrombolytic (n=1).

2.3.3 Quality assessment

The methodological quality of studies ranged from 45% to 81%, with a mean score of 67% (Table 2.2). Table 2.3 summarises average scores for each of 16 quality assessment criteria. Two studies were deemed to be low, 38 medium, and 26 high quality. The most prominent methodological weaknesses were lack of reporting reliability and validity of data measurement tools used in quantitative studies and reliability of analytical process used in qualitative studies. There was no evidence of pilot testing or user involvement across all studies. If the user involvement in the design criterion was removed from the assessment, the methodological quality of studies would range from 49% to 87% with a mean score of 72%.
<table>
<thead>
<tr>
<th>Author(s), publication year, country</th>
<th>Study objective related to this systematic review</th>
<th>Study Design</th>
<th>Data Source</th>
<th>Setting</th>
<th>Medicine(s)</th>
<th>Sample</th>
<th>Key Findings</th>
<th>Funding source and Conflict of Interest (COI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abraham et al. (2010), USA</td>
<td>To investigate if participation in clinical trials research network influences adoption of alcohol pharmacotherapies in publicly funded programmes</td>
<td>Quantitative</td>
<td>Face-to-face interviews and brief telephone interviews</td>
<td>Primary and secondary care</td>
<td>acamprosate</td>
<td>244 public programmes, 127 Clinical Trial Network (CTN) affiliated programme administrators</td>
<td>Affiliation of programmes with CTN; Percentage of master's level counsellors; Access to a prescribing physician.</td>
<td>Funding: national funding body COI: not reported</td>
</tr>
<tr>
<td>AbuDagga et al. (2014), USA</td>
<td>To identify factors associated with dabigatran versus warfarin use</td>
<td>Quantitative</td>
<td>Administrative pharmacy and medical claims database</td>
<td>Primary and secondary care</td>
<td>dabigatran</td>
<td>20,320 patients</td>
<td>Patient’s clinical and demographic characteristics; Speciality of prescriber; Patient’s health insurance plan type.</td>
<td>Funding: Daiichi Sankyo COI: one author was an employee of Daiichi Sankyo; another received payments from Daiichi Sankyo; four authors- none</td>
</tr>
<tr>
<td>Anderson et al. (2015), USA</td>
<td>To determine if conflict of interest policies influence psychiatrists’ antipsychotic prescribing and compare prescribing between academic and non-academic psychiatrists</td>
<td>Quantitative</td>
<td>IMS Health databases and physicians’ characteristics database</td>
<td>Primary and secondary care</td>
<td>Nine new and reformulated antipsychotics</td>
<td>2,464 prescribers</td>
<td>Affiliation with academic medical centres with conflict-of-interest policies; Type of prescriber (academic or non-academic).</td>
<td>Funding: national funding body COI: none</td>
</tr>
<tr>
<td>Anderson et al. (2018), USA</td>
<td>To explore characteristics of prescribers adopting new cardiovascular medicines</td>
<td>Quantitative</td>
<td>IMS Health databases</td>
<td>Primary and secondary care</td>
<td>dabigatran, aliskiren</td>
<td>5,953 physicians</td>
<td>Speciality of prescriber; Gender of prescriber; Medical school attended by prescriber.</td>
<td>Funding: national funding body COI: none</td>
</tr>
<tr>
<td>Baik et al. (2016), USA</td>
<td>To evaluate how patient characteristics are associated with the initiation of anticoagulant for patients newly diagnosed with atrial fibrillation</td>
<td>Quantitative</td>
<td>Pharmacy claims database</td>
<td>Primary and secondary care</td>
<td>dabigatran, rivaroxaban</td>
<td>17,193 patients</td>
<td>Patient clinical and demographic characteristics; Patient’s health insurance plan type; Out-of-pocket expenses- no effect.</td>
<td>Funding: national funding body COI: none</td>
</tr>
<tr>
<td>Boon et al. (2008), Belgium</td>
<td>To examine the impact of reimbursement restrictions on the choice of antiepileptic (AEDs)</td>
<td>Quantitative</td>
<td>Structured face-to-face interviews</td>
<td>Secondary care</td>
<td>16 AEDs, including old and new</td>
<td>100 neurologists</td>
<td>Reimbursement condition; Formulary restrictions.</td>
<td>Funding: GlaxoSmithKline COI: not reported</td>
</tr>
<tr>
<td>Study</td>
<td>Medications Studied</td>
<td>Study Objective</td>
<td>Study Design</td>
<td>Care Setting</td>
<td>Providers</td>
<td>Outcomes</td>
<td>Funding</td>
<td>Conflict of Interest</td>
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<tr>
<td>Bourke and Roper (2012), UK</td>
<td>escitalopram, rofecoxib, esomeprazole, desloratadine, nicotine, drospirenone and oestrogen</td>
<td>To explore the factors that shape the timing of the first prescription of six new medicines by General Practitioners (GPs)</td>
<td>Quantitative</td>
<td>Primary care</td>
<td>625 GP practices</td>
<td>Availability of nurse or clerical support; Participation in a national incentive programme to reduce prescribing costs; Previous early adoption of new medicines; GP’s prescribing portfolio size; Geographical location of GP practice.</td>
<td>Funding: not reported</td>
<td>COI: not reported</td>
</tr>
<tr>
<td>Brais et al. (2017), Canada</td>
<td>dabigatran, rivaroxaban, apixaban</td>
<td>To identify predictors of oral anticoagulant choice for patients with atrial fibrillation</td>
<td>Quantitative</td>
<td>Secondary care</td>
<td>439 patients at a single teaching hospital</td>
<td>Patient’s demographic and clinical characteristics; Speciality of prescriber.</td>
<td>Funding: Bayer Inc., and Bristol-Myers Squibb Company-Pfizer alliance</td>
<td>COI: not reported</td>
</tr>
<tr>
<td>Burden et al. (2015), Canada</td>
<td>zoledronic acid, denosumab</td>
<td>To examine the impact of formulary changes to the use of zoledronic acid</td>
<td>Quantitative</td>
<td>Primary and secondary care</td>
<td>18,226 patients</td>
<td>Formulary status change (removal of prior authorisation); Speciality of prescriber; Gender of prescriber.</td>
<td>Funding: national funding body</td>
<td>COI: none</td>
</tr>
<tr>
<td>Carracedo-Martínez et al. (2017), Spain</td>
<td>celecoxib, etoricoxib</td>
<td>To assess the impact of the removal of prior authorisation requirements for two coxibs on their use</td>
<td>Quantitative</td>
<td>Primary care</td>
<td>One health district, catchment area of 383,125 people</td>
<td>Formulary prescribing conditions (prior authorisation requirement).</td>
<td>Funding: none</td>
<td>COI: none</td>
</tr>
<tr>
<td>Chamberlain et al. (2014), UK</td>
<td>celecoxib, rofecoxib, valdecoxib</td>
<td>To explore the impact of the Cancer Drug Fund (CDF) on access to cancer medicines in England, compared with Wales</td>
<td>Quantitative</td>
<td>Secondary care</td>
<td>15 cancer medicines</td>
<td>Not stated-prescribing volumes milligrams/1000 population used</td>
<td>The CDF was associated with higher prescription volumes in England for most medicines, which NICE had rejected for some or all indications pre-CDF and for medicines, which NICE had not appraised pre-CDF, but subsequently rejected.</td>
<td>Funding: national funding body</td>
</tr>
<tr>
<td>Chitagunta et al. (2009), USA</td>
<td>celecoxib, rofecoxib, valdecoxib</td>
<td>To study the role of learning in the diffusion of three Cox-2 inhibitors before withdrawal of rofecoxib</td>
<td>Quantitative</td>
<td>Primary and secondary care</td>
<td>6,577 patients and 17,329 prescriptions</td>
<td>Advertising, news and academic articles; Socio-economic status of patient; Patient’s demographic characteristics; Patient’s health insurance plan type; Patient’s satisfaction with existing treatment.</td>
<td>Funding: not reported</td>
<td>COI: not reported</td>
</tr>
<tr>
<td>Study Authors and Year</td>
<td>USA Location</td>
<td>Study Objective</td>
<td>Study Design</td>
<td>Data Sources</td>
<td>Study Population</td>
<td>Findings</td>
<td>Funding</td>
<td>COI Notes</td>
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<tr>
<td>Chressanthis et al. (2012)</td>
<td>To examine the effect of access limits to pharmaceutical representatives on new medicines prescribing by physicians</td>
<td>Quantitative</td>
<td>IMS Health databases</td>
<td>Primary and secondary care</td>
<td>sitagliptin</td>
<td>65,131 physicians</td>
<td>Organisation restrictions to pharmaceutical representative access; Speciality and age of prescriber; Size and geographical location of organisation.</td>
<td>Funding: AstraZeneca COI: two authors were employees of AstraZeneca</td>
</tr>
<tr>
<td>Conti et al. (2012)</td>
<td>To examine how evidence of the incremental effectiveness of novel chemotherapy medicines impacts on the adoption by physicians</td>
<td>Quantitative</td>
<td>Chemotherapy order system database</td>
<td>Secondary care</td>
<td>Seven oral chemotherapy medicines</td>
<td>4,344,711 patients, 122 medical oncology practices in 35 the USA states</td>
<td>Severity of the underlying disease; Clinical trials and media reports concurrent with market launch date; Medicine effectiveness.</td>
<td>Funding: national funding body COI: not reported</td>
</tr>
<tr>
<td>DeVore et al. (2018)</td>
<td>To identify patient, provider, and practice characteristics associated with sacubitril/valsartan use</td>
<td>Quantitative</td>
<td>Observations</td>
<td>Primary and secondary care</td>
<td>sacubitril/valsartan</td>
<td>4216 patients, 121 sites across the USA</td>
<td>Patient’s clinical and demographic characteristics; Socio-economic status of patient; Patient’s health insurance plan type; Speciality of prescriber; Size of organisation; Staff composition at the organisation.</td>
<td>Funding: Novartis COI: five authors in previous receipt of funding from pharmaceutical industry; two acts as consultants to pharmaceutical industry; two were employees of Novartis</td>
</tr>
<tr>
<td>Donohue et al. (2018)</td>
<td>To estimate the effect of peer adoption of three first-in-class medications on physicians’ adoption of those medications.</td>
<td>Quantitative</td>
<td>IMS Health, insurance, and administrative claims databases</td>
<td>Primary and secondary care</td>
<td>dabigatran, sitagliptin, aliskiren</td>
<td>11,958 physicians</td>
<td>Peer influence (internal and external).</td>
<td>Funding: national funding body COI: not reported</td>
</tr>
<tr>
<td>Ducharme and Abraham (2008)</td>
<td>To examine predictors of buprenorphine adoption</td>
<td>Quantitative</td>
<td>Brief telephone interviews and survey database</td>
<td>Primary and secondary care</td>
<td>buprenorphine</td>
<td>Staff members from 49 USA states and a data set of 12,236 substance abuse treatment facilities</td>
<td>Government owned and non-profit facilities; Hospital-based programmes and opioid treatment programmes; Programmes offering detoxification services; Accredited programmes; Programmes serving adult population; Geographical location and size of programme; Programmes having at least one managed care contract; Patient’s health insurance.</td>
<td>Funding: national funding body COI: none</td>
</tr>
<tr>
<td>Authors</td>
<td>Year/Country</td>
<td>Purpose</td>
<td>Study Design</td>
<td>Setting</td>
<td>Main Medicines/Pharmacies</td>
<td>Participants</td>
<td>Funding/COI</td>
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<tr>
<td>Dybdahl et al.</td>
<td>2011, Denmark</td>
<td>To analyse associations between GPs’ clinical interests and their preference for new medicine</td>
<td>Quantitative</td>
<td>Primary care</td>
<td>Three COX-2 inhibitors and six angiotensin-II antagonists medicines</td>
<td>68 GPs</td>
<td>Continuous medical education activities.</td>
<td></td>
</tr>
<tr>
<td>Friedman et al.</td>
<td>2010, USA</td>
<td>To examine the influence of senior managers’ characteristics on the adoption of buprenorphine</td>
<td>Quantitative</td>
<td>Primary and secondary care</td>
<td>Buprenorphine</td>
<td>547 pairs of administrative directors and clinical supervisors</td>
<td>Gender, age, the length of service and views of programme directors on treatment; Affiliations and accreditation of programme; Breadth of provided medical services; Staff composition; Gender of patients.</td>
<td>Funding: national funding body COI: not reported</td>
</tr>
<tr>
<td>Fuksa et al.</td>
<td>2015, Czech Republic</td>
<td>To evaluate the overall changes in statin utilisation and expenditure with regards to the changing prescribing conditions</td>
<td>Quantitative</td>
<td>Primary and secondary care</td>
<td>Atorvastatin, Rosuvastatin</td>
<td>774,281 patients</td>
<td>Changes in formulary prescribing conditions.</td>
<td></td>
</tr>
<tr>
<td>Garjon et al.</td>
<td>2012, Spain</td>
<td>To analyse the diffusion of new medicines during the first months of use and examine the adoption between family physicians and specialists</td>
<td>Quantitative</td>
<td>Primary and secondary care</td>
<td>Cefditoren, Duloxetine, Etoricoxib, Ezetimibe, Levocetirizine, Olmesartan, Pregabalin, Tiotropium</td>
<td>1,248 physicians</td>
<td>Speciality of prescriber; Therapeutic innovation of medicine; Range of indications for medicine; Prior authorisation requirement.</td>
<td></td>
</tr>
<tr>
<td>Groves et al.</td>
<td>2010, Canada</td>
<td>To assess relationship between physicians’ characteristics and prescribing of new medicines</td>
<td>Quantitative</td>
<td>Primary and secondary care</td>
<td>Four COX-2 inhibitors and two non-selective NSAIDs medicines</td>
<td>925 physicians</td>
<td>Demographic characteristics; Speciality of prescriber; Geographical location of practice; Caseload of prescriber.</td>
<td></td>
</tr>
<tr>
<td>Haider et al.</td>
<td>2008, Sweden</td>
<td>To examine the association between educational level of patients and the use of newly marketed medicines among elderly patients</td>
<td>Quantitative</td>
<td>Primary and secondary care</td>
<td>18 newly marketed medicines with at least 350 users</td>
<td>626,258 patients</td>
<td>Patient’s educational level and gender; Number of prescribed medicines for patient; Patient’s residential area.</td>
<td></td>
</tr>
<tr>
<td>Hickson et al.</td>
<td>2019, USA</td>
<td>To describe trends over time in the initiation of the dipeptidyl peptidase-4 (DPP-4) inhibitors before and after removal of the rosiglitazone black box warning and restricted access programme</td>
<td>Quantitative</td>
<td>Primary and secondary care</td>
<td>DPP-4 inhibitors</td>
<td>280,969 patients</td>
<td>Regulatory restrictions to the use of medicines in the same category as new medicines.</td>
<td></td>
</tr>
</tbody>
</table>

Funding: not reported
COI: authors received consultant fees or/and were involved in pharmaceutical industry funded research

Funding: not reported
COI: three authors received educational fees from pharmaceutical industry

Funding: not reported
COI: not declared

Funding: not reported
COI: none

Funding: not reported
COI: one author was employee of Truven Health Analytics/IBM Watson Health
<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Objective</th>
<th>Study Design</th>
<th>Setting</th>
<th>Intervention</th>
<th>Outcome measures</th>
<th>Sample size</th>
<th>Funding/COI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirunrassamee and Ratanawijtrasisin (2009), Thailand</td>
<td>To assess access to medicines and other medical technologies under the three government health insurance schemes</td>
<td>Quantitative</td>
<td>Hospital electronic database and paper records</td>
<td>Secondary care Antiepileptic and antineoplastic lung cancer medicines</td>
<td>913 patients (antiepileptics), 33 patients (antineoplastics) ; 3 hospital sites</td>
<td>Patient’s health insurance plan type; Out-of-pocket payments.</td>
<td>Funding: not reported COI: not reported</td>
</tr>
<tr>
<td>Hsieh and Liu (2012), Taiwan</td>
<td>To explore issues surrounding utilisation of biologics in Taiwan</td>
<td>Quantitative</td>
<td>National insurance claims database</td>
<td>Secondary care</td>
<td>trastuzumab, rituximab, peginterferon-alfa-2A, etanercept</td>
<td>590 patients</td>
<td>Size of hospital; Type of hospital ownership; Patient’s clinical characteristics.</td>
</tr>
<tr>
<td>Huang et al. (2013), USA</td>
<td>To examine factors that influence doctors’ decision in initiating or switching from warfarin to dabigatran</td>
<td>Quantitative</td>
<td>Online survey</td>
<td>Secondary care</td>
<td>dabigatran</td>
<td>65 physicians</td>
<td>Cost of medicine; Patient’s socioeconomic status; Patient’s clinical characteristics; Specialty of prescriber; Experience of prescriber with the medicine; Perceived benefits of new over ‘old’ therapy.</td>
</tr>
<tr>
<td>Huskamp et al. (2013), USA</td>
<td>To examined physician adoption of second-generation antipsychotic medications and identified physician-level factors associated with early adoption</td>
<td>Quantitative</td>
<td>IMS Health prescription database</td>
<td>Primary and secondary care</td>
<td>olanzapine, quetiapine, ziprasidone, and aripiprazole</td>
<td>30,369 physicians</td>
<td>Age and gender of prescriber; Specialty of prescriber; Size and type of practice; Caseload of prescriber; Medical school location of prescriber.</td>
</tr>
<tr>
<td>Iyengar et al. (2011), USA</td>
<td>To assess the impact of social networks on the adoption of a new medicine by physicians</td>
<td>Quantitative</td>
<td>Mailed and online survey, IMS Health databases, and pharmaceutical company sales calls records</td>
<td>Primary and secondary care</td>
<td>A newly launched prescription medicine used to treat a specific type of viral infection (short and long-term)</td>
<td>185 physicians from three cities</td>
<td>Peers influence- the level of impact is shaped by peer’s usage volume and by the clinicians’ perception of their self-reported opinion leadership. Perceived leaders by colleagues adopted new medicine quicker than self-reported leaders.</td>
</tr>
<tr>
<td>Study</td>
<td>Methods</td>
<td>Design</td>
<td>Key Findings</td>
<td>Funding/COI</td>
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<tr>
<td>Karampli et al. (2020), Greece</td>
<td>Qualitative Semi-structured face-to-face interviews</td>
<td>Primary and secondary care</td>
<td>DDP-4 inhibitors, GLP-1 agonists, SGLT2 inhibitors, new oral fixed-dose combinations of glucose-lowering medications, new dosage forms</td>
<td>Funding: none COI: none</td>
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<tr>
<td>Keating et al. (2018), USA</td>
<td>Quantitative Insurance claim database</td>
<td>Secondary care</td>
<td>bevacizumab</td>
<td>Size and accreditation of organisation; Staff composition at organisation; Patient’s clinical and demographic characteristics; Patient’s socio-economic status. Funding: national funding body COI: none</td>
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<tr>
<td>Keating et al. (2020), USA</td>
<td>Quantitative Insurance claim database</td>
<td>Secondary care</td>
<td>bevacizumab</td>
<td>44,012 patients, 3,261 physicians, 51 hospital referral regions             Patient’s clinical and demographic characteristics; Patient’s socio-economic status. Funding: national funding body COI: one author received consultant fees from Grail</td>
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<td>Kennedy et al. (2020), Ireland</td>
<td>Quantitative Pharmacy claims database shapefiles of warfarin clinics and areas</td>
<td>Primary care</td>
<td>apixaban, dabigatran, edoxaban, rivaroxaban</td>
<td>Presence or absence of hospital-based warfarin clinics- no effect. Funding: national funding body COI: none</td>
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<td>Kereszturi et al. (2015), Hungary</td>
<td>Quantitative DoktorInfo prescription database</td>
<td>Secondary care</td>
<td>vildagliptin with metformin and metformin with sitagliptin combinations</td>
<td>Portfolio width and prescribing volume of prescriber; Number of patients looked after by prescriber and number of consultations per patient; Prescribing of other branded medicines; Proportion of patients treated with insulin. Funding: AXA Research Fund COI: not reported</td>
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<td>King et al. (2013), USA</td>
<td>Quantitative IMS Health database and physicians' characteristics database</td>
<td>Primary care</td>
<td>lisdexamfetamine, paliperidone, desvenlafaxine</td>
<td>Attending a medical school with an active gift restriction policy; Length of exposure to gift restriction policy. Funding: national funding body COI: none</td>
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<tr>
<td>Study</td>
<td>Title</td>
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<td>Setting</td>
<td>Key Outcomes</td>
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<tr>
<td>King and Bearman (2017), USA</td>
<td>To examine how different pharmaceutical detailing regulations and peer influence shaped medicine diffusion processes of newly marketed medicines</td>
<td>Quantitative</td>
<td>IMS Health prescription database</td>
<td>Primary care</td>
<td>lisdexamfetamine, duloxetine</td>
<td>208,072 physicians for duloxetine, 215,445 physicians for lisdexamfetamine</td>
<td>Policies limiting or banning gifts from pharmaceutical industry; Peer influence.</td>
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<tr>
<td>Knudsen et al. (2009), USA</td>
<td>To examine the adoption of buprenorphine over 2 years in community-based treatment programmes associated and not with Clinical Trials Network (CTN)</td>
<td>Quantitative</td>
<td>Telephone and face-to-face interviews</td>
<td>Primary care</td>
<td>buprenorphine</td>
<td>193 community-based treatment programmes (CTPs)</td>
<td>Involvement in CTN buprenorphine protocol development; Size of organisation; Access to prescribers; Offering other inpatient services; Type of organisation.</td>
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<tr>
<td>Lin H et al. (2011), USA</td>
<td>To explore the patterns of physician prescribing and medication choice for major depressive disorder between 1993-2007</td>
<td>Quantitative</td>
<td>National survey database</td>
<td>Primary care</td>
<td>Four antidepressant drug classes</td>
<td>125,605,444 patients</td>
<td>Patient’s health insurance type; Age of patient; Practice geographical location</td>
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<td>Lin S et al. (2011), Taiwan</td>
<td>To examine how the prescribing decisions made by psychiatrists’ colleagues influence the likelihood of the psychiatrists’ initial prescription</td>
<td>Quantitative</td>
<td>National insurance database</td>
<td>Secondary care</td>
<td>duloxetine</td>
<td>155 psychiatrists</td>
<td>Speciality of prescriber; Clinical experience of prescriber; Adoption behaviour of colleagues.</td>
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<td>Liu et al. (2011), Taiwan</td>
<td>To investigate the effect of various economic factors on the diffusion of new medicines</td>
<td>Quantitative</td>
<td>National drug claims database</td>
<td>Primary and secondary care</td>
<td>seven oral anti-glycaemic medicines</td>
<td>3,384,223 prescriptions</td>
<td>Degree of competition in the pharmaceutical and health service market; Size of the provider; Type of organisation; Disease severity; Geographical location of organisation.</td>
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<tr>
<td>Liu and Gupta (2012), USA</td>
<td>To analyse individual physicians’ adoption of a newly launched prescription medicine</td>
<td>Quantitative</td>
<td>ImpactRx market research database and TNS Media Intelligence data (journal advertising expenditure)</td>
<td>Primary and secondary care</td>
<td>A newly launched medicine from one of the largest therapeutic classes of prescription medicines in USA, novel mechanism of action</td>
<td>2,129 physicians</td>
<td>Targeted detailing, journal advertising, meetings and events sponsored by industry, peer influence, and patient requests has a positive impact. Specialists and prescribers with larger prescription volumes in the studied therapeutic class and who practice in communities with a larger percentage of patients from a White background adopted the new medicine quicker.</td>
</tr>
<tr>
<td>Study Authors</td>
<td>Study Title</td>
<td>Study Objective</td>
<td>Study Design</td>
<td>Data Sources</td>
<td>Setting</td>
<td>Prescribers/Subjects</td>
<td>Speciality of prescriber; Prescribers age; Hospital referral region; Patient’s health insurance plan type; Geographical location of organisation; Accreditation of organisation-no effect; Patient’s clinical and demograpic characteristics; Patient’s health insurance plan type-no effect; Size and accreditation of organisation and available services- no effect; National guideline publication-little/no effect.</td>
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<tr>
<td>Lo Ciganic et al.</td>
<td>To examine the physician adoption of dabigatran</td>
<td>Quantitative IMS Health database and physicians’ characteristics database</td>
<td>Primary and secondary care dabigatran</td>
<td>3,911 prescribers</td>
<td>Speciality of prescriber; Prescribers age; Hospital referral region; Patient’s health insurance plan type.</td>
<td>Funding: national funding body; university funding COI: none</td>
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<tr>
<td>Luo et al.</td>
<td>To assess the prevalence and variation in sacubitril/valsartan prescription among a real-world population with heart failure with a reduced ejection fraction</td>
<td>Quantitative National registry of hospitalised patients</td>
<td>Secondary care sacubitril/valsartan</td>
<td>21,078 patients, 241 hospital sites</td>
<td>Geographical location of organisation; Accreditation of organisation-no effect; Patient’s clinical and demographic characteristics; Patient’s health insurance plan type-no effect.</td>
<td>Funding: Novartis COI: one author was employee and three received consultant fees from Novartis; one received research funding from pharmaceutical companies</td>
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<tr>
<td>Luo et al.</td>
<td>To evaluate the early impact of this national treatment guideline update on the use of sacubitril/valsartan</td>
<td>Quantitative National registry of hospitalised patients and national hospitals survey database</td>
<td>Secondary care sacubitril/valsartan</td>
<td>7,200 patients</td>
<td>Size, location, accreditation of organisation and available services- no effect; National guideline publication- little/no effect.</td>
<td>Funding: Novartis COI: one author was employee of Novartis; four received research support from industry</td>
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<tr>
<td>Luo et al.</td>
<td>To identify hospital characteristics associated with the use of sacubitril/valsartan</td>
<td>Quantitative National registry of hospitalised patients; national hospitals survey database, US census region, insurance claim database</td>
<td>Secondary care sacubitril/valsartan</td>
<td>16,674 patients, 210 hospital sites</td>
<td>Size and accreditation of organisation-no effect; Organisation type (profit/non-profit); Geographical location of organisation; Follow-up ambulatory services-no effect.</td>
<td>Funding: Novartis COI: one author was employee of Novartis; three authors received research support from pharmaceutical companies</td>
<td></td>
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<tr>
<td>Manchanda et al.</td>
<td>To explore impact of marketing and interpersonal communication on the adoption of new medicine in two unrelated markets</td>
<td>Mixed-methods Pharmacy audit database, pharmaceutical company marketing records, interviews</td>
<td>Primary and secondary care A new medicine from an important medicine category</td>
<td>466 physicians</td>
<td>Pharmaceutical industry targeted communication; Detailing, detailing stock, and sampling stock by pharmaceutical industry; Peer influence; Direct advertising to patients-no effect.</td>
<td>Funding: university funding COI: not reported</td>
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<tr>
<td>Martin et al.</td>
<td>To explore the barriers to the diffusion of newly released oral targeted therapies dedicated to metastatic breast cancer</td>
<td>Qualitative Semi-structured face-to-face interviews</td>
<td>Secondary care everolimus</td>
<td>40 physicians</td>
<td>Amount of new information to be acquired about the medicine; Lack of organisation in patient management; Time required to manage oral cancer treatments; Prescriber’s prescribing habits; No clear position of the new medicine in the therapeutic strategy; Lack of staff.</td>
<td>Funding: Odyssea association COI: none</td>
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<td>Study</td>
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<td>Study Design</td>
<td>Setting</td>
<td>Intervention</td>
<td>Sample Size</td>
<td>Factors Influencing Prescribing</td>
<td>Funding/COI</td>
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<tr>
<td>Murphy et al. (2018), Ireland</td>
<td>To explore factors that influence general practitioners prescribing of direct oral anticoagulants</td>
<td>Quantitative</td>
<td>Postal survey</td>
<td>Primary care</td>
<td>apixaban, dabigatran, edoxaban, rivaroxaban</td>
<td>221 general practitioners</td>
<td>Hospital colleagues’ influence; Local and national guidelines; Conferences and journal articles; Clinical and demographic characteristics of patient; Perceived efficacy of medicine; Monitoring requirements; Size of practice.</td>
</tr>
<tr>
<td>Netherland et al. (2009), USA</td>
<td>To examine factors affecting willingness to adopt buprenorphine by physicians</td>
<td>Quantitative</td>
<td>On-site and online surveys</td>
<td>Primary care</td>
<td>buprenorphine</td>
<td>172 prescribers, two national programmes</td>
<td>Training of clinical staff on new medicine; Access to other services and treatments; Presence of effective referral system for alternative treatment; Adequate time per visit; Patients’ concerns about medicine; Availability of clinical guidelines and medicine; Reimbursement for consultation; Record keeping requirements; Access to an expert prescriber; Gender and ethnicity of prescriber; Experience and speciality of prescriber.</td>
</tr>
<tr>
<td>Ohl et al. (2013), USA</td>
<td>To determine rural-urban variation in adoption of raltegravir amongst in national Veterans Affairs healthcare</td>
<td>Quantitative</td>
<td>Health care and residence databases</td>
<td>Primary and secondary care</td>
<td>raltegravir</td>
<td>1,222 patients</td>
<td>Residential area of patient; Patient’s clinical and demographic characteristics; Previous use of antiretroviral medicines.</td>
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<tr>
<td>Ohlsson et al. (2009), Sweden</td>
<td>To investigate determinants of early adoption of rosuvastatin</td>
<td>Quantitative</td>
<td>National drug register</td>
<td>Primary care</td>
<td>rosuvastatin</td>
<td>73,547 prescriptions from 170 health care practices</td>
<td>Type of ownership; Existence of strong therapeutic traditions; Socioeconomic status of patient.</td>
</tr>
<tr>
<td>Patel et al. (2015), USA</td>
<td>To characterise the prevalence, patterns, and predictors of direct oral anticoagulants versus warfarin therapy at discharge among atrial fibrillation patients hospitalised with ischemic stroke or transient ischemic attack</td>
<td>Quantitative</td>
<td>National stroke database</td>
<td>Secondary care</td>
<td>dabigatran, rivaroxaban</td>
<td>61,655 patients from 1,542 hospitals</td>
<td>Patient’s clinical characteristics; Ambulatory status of patient; Discharge destination; Patient’s health insurance plan type.</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Objective</td>
<td>Study Design</td>
<td>Setting</td>
<td>Sample Size</td>
<td>Data Sources</td>
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<tr>
<td>Potpara et al. (2017), Balkan countries</td>
<td>Balkan countries</td>
<td>To explore the use of direct oral anticoagulants in seven Balkan countries</td>
<td>Quantitative Online survey</td>
<td>Secondary care</td>
<td>dabigatran, rivaroxaban, apixaban</td>
<td>2,663 patients from 49 centres</td>
<td>Speciality of prescriber; Patient’s clinical characteristics; Atrial fibrillation treatment strategy; Hospital-based centres; Previous use of oral anticoagulants.</td>
</tr>
<tr>
<td>Rodwin et al. (2020), USA</td>
<td>USA</td>
<td>To examine patient and hospital-level factors associated with prasugrel and ticagrelor use in acute myocardial infarction</td>
<td>Quantitative National hospital registry for patients with myocardial infarction</td>
<td>Secondary care</td>
<td>prasugrel, ticagrelor</td>
<td>362,354 patients, 801 hospitals</td>
<td>Patient’s clinical and demographic characteristics; Patient’s health insurance plan type; Number of patients treated in hospital; Geographical location and accreditation of organisation; Speed of adoption of previous innovation.</td>
</tr>
<tr>
<td>Sato et al. (2012), Japan</td>
<td>Japan</td>
<td>To assess the impact of the sitagliptin regulatory safety alert on the prescribing behaviour</td>
<td>Quantitative Prescription data from 300 pharmacies</td>
<td>Primary and secondary care</td>
<td>sitagliptin</td>
<td>87,678 patients</td>
<td>Size of hospital; Speciality of prescriber; Safety alert.</td>
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<td>Savage et al. (2012), USA</td>
<td>USA</td>
<td>To examine the extent to which programmes’ interorganisational institutional and resource-based linkages predict the likelihood of being an earlier adopter, later adopter, or non-adopter of buprenorphine</td>
<td>Quantitative Face-to-face interviews and brief telephone interviews</td>
<td>Primary and secondary care</td>
<td>buprenorphine</td>
<td>345 privately funded substance abuse treatment programmes</td>
<td>Membership in national and regional associations; Detailing activities by pharmaceutical companies; Use of National Institute on Drug Abuse website as an information source.</td>
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<tr>
<td>Scholten et al. (2015), Germany</td>
<td>Germany</td>
<td>To examine the factors at the organisational level that influence the implementation of systemic thrombolysis in stroke patients.</td>
<td>Quantitative Hospital structure quality reports registry</td>
<td>Secondary care</td>
<td>alteplase</td>
<td>286 hospitals</td>
<td>Existence of stroke unit; Hospital size.</td>
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<tr>
<td>Authors</td>
<td>Duration</td>
<td>Country</td>
<td>Aim</td>
<td>Study Design</td>
<td>Setting</td>
<td>Sample Size</td>
<td>Outcomes</td>
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<tr>
<td>Steinberg et al. (2013), USA</td>
<td>To identify patient and/or provider factors associated with the use of dabigatran in patients with atrial fibrillation</td>
<td>Quantitative</td>
<td>National registry for outpatients with atrial fibrillation</td>
<td>Secondary care</td>
<td>dabigatran</td>
<td>8,794 patients, 176 sites</td>
<td>Patient’s clinical and demographic characteristics; Patient’s health insurance plan type; Education level of patient; Current antiarrhythmic use; Speciality of prescriber.</td>
</tr>
<tr>
<td>Tanislav et al (2018), Germany</td>
<td>To investigate oral anticoagulation in stroke patients documented in a nationwide registry</td>
<td>Quantitative</td>
<td>National hospital quality registry</td>
<td>Secondary care</td>
<td>apixaban, dabigatran, edoxaban, rivaroxaban</td>
<td>3,813 patients</td>
<td>Treatment on stroke unit; Patient’s clinical and demographic characteristics; Previous oral anticoagulant/antiplatelet use.</td>
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<tr>
<td>Tobin et al (2008), Australia</td>
<td>To identify the factors that influence prescribing of new medicines among general practitioners, endocrinologists and psychiatrists</td>
<td>Qualitative</td>
<td>Focus groups with a semi-structure interview guide</td>
<td>Primary and secondary care</td>
<td>Medicine that has in the past 1–2 years been in Pharmaceutical Benefits Scheme (PBS) listed, or released to the market, or a new chemical entity</td>
<td>21 prescribers</td>
<td>Socioeconomic status of patient; Clinical need for medicine; New medicine’s attributes: adverse effects, safety, efficacy; Listing of medicine in PBS; Peer influence; Prescriber’s familiarity with the therapeutic area; Prescriber’s knowledge of the medicine.</td>
</tr>
<tr>
<td>Tsai et al (2010), Taiwan</td>
<td>To examine factors affecting thiazolidinediones penetration into Taiwan’s hospitals</td>
<td>Quantitative</td>
<td>National health insurance database</td>
<td>Secondary care</td>
<td>pioglitazone, rosiglitazone</td>
<td>580 hospitals</td>
<td>Degree of competition in the pharmaceutical market; Type of hospital; Type of ownership of hospital; Geographical location of hospital; Cost of medicines; Prescribing volume of diabetic medicines by hospital.</td>
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<tr>
<td>Wang et al. (2010), Taiwan</td>
<td>To determine if socioeconomic status impacts adoption of newly reimbursed non-steroidal anti-inflammatory medicines under a universal health insurance programme</td>
<td>Quantitative</td>
<td>Eight different electronic databases</td>
<td>Primary and secondary care</td>
<td>rofecoxib, celecoxib, nimesulide</td>
<td>875 patients</td>
<td>Patient’s clinical and demographic characteristics; Patient’s socio-economic status; Patient’s habits of health-care utilisation.</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Objective</td>
<td>Research Design</td>
<td>Setting</td>
<td>Sample Size</td>
<td>Methods</td>
<td>Funding</td>
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<td>Weir et al. (2012), Canada</td>
<td>To explore the impacts of formulary listing changes and regulatory agency warnings on the use of erythropoiesis-stimulating agents in cancer patients</td>
<td>Quantitative</td>
<td>Prescription and physician characteristics databases, province people registry</td>
<td>Secondary care</td>
<td>Three erythropoiesis-stimulating agents</td>
<td>171,967 patients</td>
<td>Formulary changes in reducing or removing restrictions for use; Safety warnings from regulatory agencies.</td>
</tr>
<tr>
<td>Wen et al. (2011), Taiwan</td>
<td>To characterise how a new medicine class for diabetes mellitus diffused in the health care market</td>
<td>Quantitative</td>
<td>National insurance claim database</td>
<td>Secondary care</td>
<td>rosiglitazone, pioglitazone</td>
<td>580 hospitals</td>
<td>Accreditation and type of hospital; Type of ownership of hospital; Degree of competition in the pharmaceutical market; Geographical location of hospital; Number of prescribers prescribing these medicines; Prior anti-diabetic prescription capacity.</td>
</tr>
<tr>
<td>Zhang et al. (2019), Australia</td>
<td>To evaluate how physicians’ risk preferences and personality affects their decisions to adopt new prescription medicines</td>
<td>Quantitative</td>
<td>Database of a national panel survey of medical practitioners, insurance claim database</td>
<td>Primary care</td>
<td>apixaban, dabigatran, rivaroxaban</td>
<td>576 GPs</td>
<td>Socio-demographic characteristics of prescriber; Prescribing volume; Willingness to take clinical risks; Employment status in the GP practice; Time spent in consultations; Location of GP practice; GP practice affiliations and social practice characteristics-no effect; Patient’s demographic characteristics; Patient’s socio-economic status.</td>
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</table>
Table 2.2 Methodological quality of included studies using the QATSDD tool.

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<td>1. Explicit theoretical framework</td>
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<td>2. Statement of aims/objectives in main body of report</td>
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<td>3. Clear description of research setting</td>
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<td>4. Evidence of sample size considered in terms of analysis</td>
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<td>5. Representative sample of target group of a reasonable size</td>
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<td>6. Description of procedure for data collection</td>
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<td>7. Rationale for choice of data collection tool(s)</td>
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<td>8. Detailed recruitment data</td>
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<td>9. QUANTITATIVE only: Statistical Assessment of reliability and validity of measurement tool(s)</td>
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Table 2.3 Scores summary for the 16 criteria used to assess the quality for quantitative and qualitative studies. The score of mixed-methods study (n=1) was not included.

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<th>Standard deviation</th>
<th>% maximum of the possible score achieved</th>
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<td>0.9</td>
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<td>2.7</td>
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<td>14. Assessment of reliability of analytical process (Qualitative studies only)</td>
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2.3.4 Reported factors affecting the uptake of new medicines

Factors affecting the uptake of new medicines were grouped into five thematic areas: patient, prescriber, medicine, organisational, and external environment factors. The thematic area(s) identified in each included study are shown in Table 2.4. External environment, organisational, patient, and prescriber factors were reported most frequently (n=36, n=34, n=31, and n=29 studies respectively) and medicine factors (n=18) were the least. Table 2.5 presents a summary of factors affecting the uptake of new medicines referred to in the reviewed studies.

Table 2.4 Summary of thematic areas identified in the included studies.

<table>
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<tr>
<th>Study</th>
<th>Prescriber factors</th>
<th>Patient factors</th>
<th>Medicine factors</th>
<th>Organisational factors</th>
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2.3.4.1 Patient factors

Thirty-one studies identified factors related to patient characteristics that affected the use of new medicines. Patient factors were classed into patient demographic characteristics, socio-economic status, health status, and engagement with treatment.

**Demographic characteristics** (n=21). Studies reported mixed results of patients’ age, gender, and ethnicity impact on the uptake of new medicines. Some prescribers tended to prescribe new medicines to patients who were younger (AbuDagga et al. 2014; Brais et al. 2017; DeVore et al. 2018; Keating et al. 2018; Keating et al. 2020; Lin H et al. 2011; Luo et al. 2017; Ohlsson et al. 2009; Patel et al. 2015; Rodwin et al. 2020; Steinberg et al. 2013), male (AbuDagga et al. 2014; Patel et al. 2015; Rodwin et al. 2020; Steinberg et al. 2013), female (Wang et al. 2010), or White ethnicity (Liu and Gupta 2012). Others observed use of new medicine in older patients (Chitagunta et al. 2009; Baik et al. 2016; Ohl et al. 2013; Wang et al. 2010; Zhang et al. 2019), the mixed impact of ethnicity (Baik et al. 2016; DeVore et al. 2018; Keating et al. 2018; Patel et
al. 2015; Rodwin et al. 2020; Steinberg et al. 2013) or suggested that patients’ age (Liu et al. 2011; Potpara et al. 2017; Tanislav et al. 2018), gender (Brais et al. 2017; Burden et al. 2015; Lin H et al. 2011; Liu et al. 2011; Potpara et al. 2017; Ohlsson et al. 2009; Steinberg et al. 2013), and ethnicity (Lin H et al. 2011; Ohl et al. 2013; Wang et al. 2010) had no impact on prescribing decisions. Studies were medium to high quality and one study (Tanislav et al. 2018) was low quality.

Socio-economic status (n=21). Some prescribers reported that patients’ socioeconomic factors (Murphy et al. 2018), which included education, income, health insurance plan, and residential area, influenced their prescribing decisions. Some findings suggested patients with a higher level of education were more likely to receive new medicines (Chitagunta et al. 2009; DeVore et al. 2018; Haider et al. 2008; Steinberg et al. 2018), regardless of their age, gender, education, type of residential area, number of medicines used, and comorbidity (Haider et al. 2008). However, one study (Wang et al. 2010) observed no impact of patient education level. All studies were of high quality. Prescribers also considered the affordability of new medicines by patients (Karampli et al. 2020). Some studies suggested patients with higher income or ability to pay out-of-pocket expenses were more likely to receive a new medicine (AbuDagga et al. 2014; Chitagunta et al. 2009; Hirunrassamee and Ratanawijitrasin 2009; Huang et al. 2013; Keating et al. 2018; Ohlsson et al. 2009; Tobin et al. 2008; Wang et al. 2010; Zhang et al. 2019), but one study observed no difference (Baik et al. 2016). Only three studies were high quality (Chitagunta et al. 2009; Ohlsson et al. 2009; Wang et al. 2010). Furthermore, the type of patient’s health insurance plan was a factor influencing the use of new medicines. Patients with private health insurance plans covering prescription medicines and medical care services were reported to have greater access to new medicines (AbuDagga et al. 2014; Baik et al. 2016; DeVore et al. 2018; Hirunrassamee and Ratanawijitrasin 2009; Lin H et al. 2011; Lo-Ciganic et al. 2016; Patel et al. 2015; Rodwin et al. 2020; Steinberg et al. 2013); two studies were high quality (DeVore et al. 2018; Steinberg et al. 2013). Lastly, some studies indicated that patients living in a capital city (Haider et al. 2008), urban (Ohl et al. 2013), or more affluent areas (Zhang et al. 2019) were more likely to receive new medicines; two studies were high quality (Ohl et al. 2013; Haider et al. 2008).

Health status (n=21). Prescribers highlighted patients’ clinical characteristics and comorbidities that influenced new medicines use (Karampli et al. 2020). Some prescribers reported prescribing new medicines for patients with more severe disease
(Conti et al. 2012; DeVore et al. 2018; Hsieh and Liu 2012; Luo et al. 2017; Wang et al. 2010) or polypharmacy (AbuDagga et al. 2014; Baik et al. 2016; Haider et al. 2008); five studies were high quality (Conti et al. 2012; DeVore et al. 2008; Haider et al. 2008; Hsieh and Liu 2012; Wang et al. 2010). Other low to high-quality studies reported new medicines use in patients with fewer comorbidities, or less severe conditions (AbuDagga et al. 2014; Brais et al. 2017; Keating et al. 2018; Patel et al. 2015; Potpara et al. 2017; Rodwin et al. 2020; Steinberg et al. 2013; Tanislav et al. 2018), and no polypharmacy or concomitant use of medicines increasing the risk of side effects (Brais et al. 2017; Patel et al. 2015; Potpara et al. 2017; Tanilav et al. 2018). Medium to high-quality studies reported patient’s poor response to current treatment encouraged (Chitagunta et al. 2009; Huang et al. 2013; Tobin et al. 2008) and patient’s satisfaction with the existing treatment discouraged new medicine use (Chitagunta et al. 2009). At the same time, learning from patients’ satisfaction with a new medicine encouraged prescribers to use more of that new medicine for other patients, thus increased prescriber’s confidence in using the new medicine (Chitagunta et al. 2009).

Patient engagement with treatment (n=5). Some prescribers stated that patients’ request for a new medicine (Huang et al. 2013; Liu and Gupta 2012; Tobin et al. 2008) and interest in it (Netherland et al. 2009), adherence to current treatment (Karampli et al. 2020; Tobin et al. 2008) and monitoring (Huang et al. 2013) influenced prescribing decisions. Some prescribers described aiming for shared decision-making, thus patients’ therapy preference and compatibility with their lifestyle (Karampli et al. 2020) shaped prescribing decisions. Only one study was high quality (Liu and Gupta 2012).

2.3.4.2 Prescriber factors

Twenty-nine studies identified factors related to prescriber characteristics influencing the use of new medicines. These factors included socio-demographic characteristics of the prescriber, scope of expertise, and knowledge and prescribing habits.

Socio-demographic characteristics (n=11). Medium to high-quality studies suggested younger (Chressanthis et al. 2012; Huskamp et al. 2013; Kennedy et al. 2020; Lo-Ciganic et al. 2016) or older (Bourke and Roper 2012; Groves et al. 2010), male (Anderson et al. 2018; Groves et al. 2010; Huskamp et al. 2013; Zhang et al. 2019), graduating from a top 20 medical (Anderson et al. 2018; Lo-Ciganic et al. 2016) or foreign medical school (Huskamp et al. 2013) prescribers were earlier adopters. Another medium to high-quality studies reported that age (Burden et al. 2015; Groves et al. 2010; Huskamp et al. 2013), gender (Burden et al. 2015; Lo-Ciganic et al. 2016),
prescribers’ length of practice (DeVore et al. 2018; Zhang et al. 2019), graduating from a top 20 medical school (Huskamp et al. 2013; Lo-Ciganic et al. 2016) did not influence prescribing decisions. A medium-quality study indicated general practitioners’ (GPs) who were principal or partner in practice were more likely to use new medicines than employee GPs (Zhang et al. 2019).

**Scope of expertise (n=23).** Thirteen studies indicated specialist prescribers adopted new medicines quicker than their other or primary care colleagues (AbuDagga et al. 2014; Anderson et al. 2018; Brais et al. 2017; Chressanthis et al. 2012; Garjon et al. 2012; Huang et al. 2013; Huskamp et al. 2013; Lin S et al. 2011; Liu and Gupta 2012; Lo-Ciganic et al. 2016; Potpara et al. 2017; Steinberg et al. 2013) but only three were high quality (Anderson et al. 2018; Liu and Gupta 2012; Steinberg et al. 2013). However, four studies observed the opposite - primary care prescribers were earlier adopters of antidiabetic medicines (Sato et al. 2012), bisphosphonates (Burden et al. 2015), cyclooxygenase-2 inhibitors (Groves et al. 2010), and one of nine studied antipsychotic medicines (Huskamp et al. 2013). One study concluded there was no difference (DeVore et al. 2019). A high-quality study observed the clinical interest of primary care prescribers did not influence new medicine prescribing from the same clinical area (Dybdhal et al. 2011). Increasing total prescribing volume (Huskamp et al. 2013; Kereszturi et al. 2015; Zhang et al. 2019) or greater prescribing portfolio breadth (Bourke and Roper 2012; Kereszturi et al. 2015) in medium-quality studies, prescribing multiple medicines for the same condition (Wen et al. 2011) or larger prescription volume in the same therapeutic class (Liu and Gupta 2012) in high-quality studies were suggested to increase adoption of new medicines. Also, a high-quality study observed non-academic prescribers were more likely to use new and reformulated antipsychotics (Anderson et al. 2015).

**Knowledge and prescribing habits (n=10).** Medium-quality studies suggested prescribers’ previous experience and knowledge of using new medicines increased their use (Huang et al. 2013; Martin et al. 2017; Murphy et al. 2018; Netherland et al. 2009; Tobin et al. 2008; Zhang et al. 2020), whereas lack of knowledge and confidence delayed or prevented use (Karampli et al. 2020; Martin et al. 2017). Some prescribers commented that an overwhelming amount of new information for new medicines prescribing discouraged their use (Martin et al. 2017). A high-quality study observed that continuing medical education activities supported prescribing of new medicine in one of two studied therapeutic areas (Dybdhal et al. 2011). In medium-quality studies,
prescribers classed as early adopters in the past (Bourke and Roper 2012), more likely to take clinical risks (Zhang et al. 2019) or spend less time in patient consultations (Zhang et al. 2019) tended to use new medicines quicker.

2.3.4.3 Medicine factors

Eighteen studies identified at least one medicine related factor that influenced the use of new medicines. The medicine-level factors included attributes of new medicine(s) such as efficacy, safety profile, cost, therapeutic innovation of new medicine, and medicine administrative burden.

Efficacy (n=6). Some prescribers stated relative effectiveness of a new medicine influenced their prescribing decisions in medium-quality studies (Karampli et al. 2020; Murphy et al. 2018; Netherland et al. 2009; Tobin et al. 2008; Zhang et al. 2020). A high-quality study, focusing on novel chemotherapies, suggested that perceived better quality rather than incremental effectiveness influenced new medicine use (Conti et al. 2012).

Safety profile (n=9). Some prescribers reported that concerns over adverse effects (Huang et al. 2013; Karampli et al. 2020; Murphy et al. 2018; Tobin et al. 2008; Zhang et al. 2020) and unknown long-term risks (Karampli et al. 2020) discouraged prescribing of new medicines. Less interactions with other medicines or food (Huang et al. 2013; Murphy et al. 2018; Tobin et al. 2008), and less reported adverse effects (Huang et al. 2013) compared to existing treatments encouraged the uptake. All were medium-quality studies. The safety of new medicines was also monitored after their marketing authorisation with their use in practice by both adopters and non-adopters (Karampli et al. 2020). Medium to high-quality studies observed that national safety reports, e.g. Food and Drug Administration, highlighting safety concerns contributed to the hesitancy of some prescribers to use new medicines (Hickson et al. 2019; Weir et al. 2012). Also, a high-quality study suggested that scientific articles rather than safety alerts influenced prescribing behaviours as safety concerns would be first reported in the scientific literature (Chitagunta et al. 2009). Another medium-quality study suggested safety concerns with an existing class of medicines encouraged prescribers to use new medicines from a therapeutically different class (Hickson et al. 2019).

Cost (n=9). Some prescribers reported a higher unit cost of a new medicine over existing therapy was a barrier for its use (Huang et al. 2013; Karampli et al. 2020; Murphy et al. 2018; Tobin et al. 2008; Zhang et al. 2020). However, a proportion of
prescribers did not consider a medicine’s cost in their prescribing decisions (Huang et al. 2013; Murphy et al. 2018; Zhang et al. 2020). The unit cost of the new medicine was perceived differently by prescribers and patients. Patients appeared willing to pay more if the new medicine was in their best interest (Tobin et al. 2008). In contrast, prescribers considered the patient’s ability to pay out of pocket costs (AbuDagga et al. 2014; Hirunrassamee and Ratanawijitrasin 2009; Huang et al. 2013; Karampli et al. 2020; Ohlsson et al. 2009; Wang et al. 2010), which could affect patients’ adherence to therapy and affordability of future prescriber’s visits (Karampli et al. 2020). Some prescribers also discussed their role in containing spending of social insurance, although others thought cost-savings to public spending was not a prescriber’s job (Karampli et al. 2020). Only two studies were high quality (Ohlsson et al. 2009; Wang et al. 2010).

*Therapeutic innovation* (n=5). Two studies suggested new medicines (Garjon et al. 2012) or reformulations (Huskamp et al. 2013), perceived as having therapeutic innovation, were adopted quicker than medicines without. Another study indicated the availability of more medicines within the same therapeutic category (i.e., higher competition) had a negative impact on new medicines entering the same category use (Liu et al. 2011). Some prescribers reported considering a new medicine’s relative clinical benefits other than safety, efficacy, or cost over existing treatment (Karampli et al. 2020; Tobin et al. 2008). For instance, a positive effect on patient’s weight, comorbidities, and cardiovascular protection by new antidiabetic medicines (Karampli et al. 2020). All studies were medium quality.

*Medicine administrative burden* (n=5). Some prescribers stated the ease of administration (Tobin et al. 2008) or use (Karampli et al. 2020) of the medicine facilitated its uptake. Another study observed that the increased complexity of taking a new medicine, e.g. twice a day, was a barrier to a minority of prescribers (Huang et al. 2013). The majority of prescribers in the case of oral anticoagulants reported reduced monitoring or clinic visits encouraged their use (Huang et al. 2013; Murphy et al. 2018). Also, concerns about the difficulty to initiate new medicines negatively affected the willingness of some prescribers to use them, especially if less experienced prescribers (Netherland et al. 2009). All studies were medium quality.

**2.3.4.4 Organisation factors**

Thirty-four studies identified at least one organisational factor affecting the use of new medicines. These were grouped into organisation’s ownership status, teaching status,
size, location, available services and resources, staff composition, and care co-
ordination and quality.

Ownership status (n=10). Four high (Ducharme and Abraham 2008; Ohlsson et al.
2009; Tsai et al. 2010; Wen et al. 2011) and three medium-quality (Knudsen et al.
2009; Liu et al. 2011; Luo et al. 2019) studies suggested private, rather than public
organisations, were more likely to use new medicines. Amongst private organisations,
for-profit treatment programmes were more likely to offer new medicines (Ducharme
and Abraham 2008; Knudsen et al. 2009). In contrast, medium to high-quality studies
observed public organisations having greater use of new medicines (Abraham et al.
2010; Hsieh and Liu 2012) or the ownership status did not influence the uptake (Luo
et al. 2018).

Teaching status (n=8). Six medium (Kereszturi et al. 2015; Luo et al. 2017; Luo et al.
2018; Luo et al. 2019; Patel et al. 2015; Potpara et al. 2017) and one high-quality
(Scholten et al. 2015) studies observed no difference in the uptake of new medicines
between teaching and non-teaching hospitals. One medium-quality study, however,
suggested a lower likelihood of new medicine use at a teaching hospital (Rodwin et al.
2020).

Size (n=17). Six high (DeVore et al. 2018; Ducharme and Abraham 2008; Hsieh and
Liu 2012; Tsai et al. 2010; Wang et al. 2010; Wen et al. 2011) and five medium-quality
(Huskamp et al. 2013; Keating et al. 2018; Knudsen et al. 2009; Liu et al. 2011; Murphy
et al. 2018) studies indicated larger hospitals or practices were more likely to use new
medicines. Other medium to high-quality studies observed it for smaller (Chressanthis
et al. 2012; Sato et al. 2012) or medium sized (Scholten et al. 2015) organisations.
Also, three medium-quality studies suggested organisation size did not influence the
uptake (Luo et al. 2019; Patel et al. 2015; Savage et al. 2012).

Location (n=16). In some medium to high-quality studies, organisations in urban areas
(Bourke and Roper 2012; Ducharme and Abraham 2008; Potpara et al. 2017), rural
locations (Patel et al. 2015; Zhang et al. 2019), or in areas with fewer GPs (Zhang et
al. 2019) were observed to have higher use of new medicines. Also, nine studies
observed regional variation in prescribing of new medicines (Liu et al. 2011; Luo et al.
2017; Luo et al. 2019; Patel et al. 2015; Rodwin et al. 2020; Tsai et al. 2010; Zhang et
al. 2019). Five medium to high-quality studies reported geographical location having
no impact on the uptake (Bourke and Roper 2012; Luo et al. 2017; Ohlsson et al. 2009;
Patel et al. 2015; Scholten et al. 2015).
Available services and resources (n=17). In some cases, organisations providing or having access to related supportive services were more likely to adopt new medicines (Ducharme and Abraham 2008; Friedman et al. 2010; Knudsen et al. 2009; Netherland et al. 2009; Savage et al. 2012; Scholten et al. 2015; Tanislav et al. 2018); two were high (Netherland et al. 2009; Scholten et al. 2015) and one low-quality (Tanislav et al. 2018) studies. For instance, detoxification, mental health services, or substance abuse counselling services for buprenorphine (Ducharme and Abraham 2008; Knudsen et al. 2009; Netherland et al. 2009; Savage et al. 2012) or stroke units for alteplase and direct oral anticoagulants (Scholten et al. 2015; Tanislav et al. 2018) were reported to facilitate the uptake. In other cases, supporting services such as the availability of heart failure clinics (DeVore et al. 2018) or follow up after hospitalisation (Luo et al. 2019) for sacubitril/valsartan, availability of hospital-based anticoagulant monitoring clinics for direct oral anticoagulants (Kennedy et al. 2020), or presence of dispensing services within general practices (Bourke and Roper 2012) had no impact. Also, prescribers reported lack of adequate time per patient visit acted as a barrier (Netherland et al. 2009; Martin et al. 2017), especially for less experienced prescribers (Netherland et al. 2009). Furthermore, some primary care clinicians suggested secondary care colleagues had more learning opportunities available (e.g. participation in clinical trials, education, and learning, access to more patients) supporting new medicine use (Karampli et al. 2020).

Staff composition (n=9). Medium-quality studies indicated that lack of specialist prescribers was a barrier to new medicine use (Abraham et al. 2010; Friedman et al. 2010; Huskamp et al. 2013; Keating et al. 2018; Knudsen et al. 2009; Martin et al. 2017). For instance, organisations with more qualified staff (Abraham et al. 2010) and GPs with hospital experience (Lin S et al. 2011) were reported to adopt some of the studied medicines quicker. A high-quality study reported that organisations with higher numbers of nurses, and healthcare professionals with a generalist medical education, were more likely to use new medicines and the number of specialist prescribers had no influence (DeVore et al. 2018). Another medium-quality study reported the presence of clerical and nursing staff to have limited to no impact on the uptake (Bourke and Roper 2012).

Care co-ordination and quality (n=3). Some prescribers suggested that lack of organisation and fragmentation in the provision of patient care (Martin et al. 2017), and non-clinical activities of care co-ordination, such as additional record-keeping
requirements (Netherland et al. 2009) were barriers to new medicine use. A study looking at heart failure treatment observed lower uptake of a new medicine within hospitals scoring higher on non-heart failure service quality measures (Luo et al. 2019). All studies were medium quality.

### 2.3.4.5 External environment factors

Thirty-six studies looked at external environment factors affecting the uptake of new medicines. External environment factors were classed into pharmaceutical detailing, reimbursement conditions and formulary status, peer influence, information sources, guidelines, and organisation affiliations.

**Pharmaceutical detailing (n=11).** The pharmaceutical industry was seen to promote awareness of new medicines through pharmaceutical detailing (pharmaceutical marketing aimed at prescribers) and indirectly through conferences, educational events, and advertisements in academic and professional journals (Liu and Gupta 2012; Karampli et al. 2020; Tobin et al. 2008). Prescribers in medium-quality studies had mixed views on its impact on their prescribing decisions (Karampli et al. 2020; Murphy et al. 2018; Tobin et al. 2008) with some reporting pharmaceutical representatives as one of their main information sources about new medicines (Karampli et al. 2020). Three studies in the USA indicated that current and/or past detailing with or without distribution of free samples had a positive impact on new medicine uptake (Liu and Gupta 2012; Machanda et al. 2008; Savage et al. 2012); two studies were high quality (Liu and Gupta 2012; Manchanda et al. 2008). Also, organisations or areas with restricted access to pharmaceutical detailing or marketing regulation policies in place (e.g. ban of gifts, disclosure policy) had lower and slower uptake of new medicines (Anderson et al. 2015; Chressanthis et al. 2012; King et al. 2013; Machanda et al. 2008), especially among primary care prescribers (Chressanthis et al. 2012); two studies were high quality (Anderson et al. 2015; Machanda et al. 2008). A high-quality study suggested gift restrictions having a greater negative impact than disclosure policies (Machanda et al. 2008). Another high-quality study indicated that prescribers completing training at medical schools with active policies restricting access to the pharmaceutical industry were less likely to use new medicines (King and Bearman 2017). A medium-quality study suggested that prescribers with very low access to pharmaceutical detailing were slower in changing their prescribing behaviour when negative information about new medicines was released (Chressanthis et al. 2012). Lastly, a high-quality study reported direct-to-
consumer advertising aimed at patients did not influence the uptake (Machanda et al. 2008).

**Reimbursement conditions and formulary status** (n=13). Nine studies suggested that reimbursement conditions for a medicine influenced the use of new medicines (Anderson et al. 2015; Boon et al. 2008; Burden et al. 2015; Carracedo-Martinez et al. 2017; Chamberlain et al. 2014; Fuksa et al. 2015; Karampli et al. 2020; Tobin et al. 2008; Weir et al. 2012); two high (Burden et al. 2015; Weir et al. 2012) and one low-quality (Carracedo-Martinez et al. 2017) study. Formulary or reimbursement restrictions (Karampli et al. 2020; Tobin et al. 2009) or cost-control regulatory measures (Anderson et al. 2015; Karampli et al. 2020) were suggested to have a negative impact on new medicine use. Removing reimbursement restrictions such as a requirement of prior authorisation (Burden et al. 2015; Carracedo-Martinez et al. 2017), specialist use only in secondary care (Fuksa et al. 2015), only as second-line therapy (Boon et al. 2008; Weir et al. 2012), or providing reimbursement for medicines excluded from a national formulary (Chamberlain et al. 2014) were suggested to support new medicine use. The inclusion of new medicines in formularies (e.g. public insurance, regional, local, national) was reported to facilitate their use (Ducharme and Abraham 2008; Tobin et al. 2008) with one study being high quality (Ducharme and Abraham 2008). Also, medium to high-quality studies suggested financial incentives to reduce prescribing costs had limited to no impact on the uptake of new medicines already included in formularies (Bourke and Rope 2012; Conti et al. 2012).

**Peer influence (internal and external)** (n=14). Some prescribers indicated that their peers' adoption of new medicines positively influenced their prescribing behaviour of new medicines in eight high (Iyenger et al. 2011; Keating et al. 2020; King and Bearman 2017; Liu and Gupta 2012; Manchanda et al. 2008; Ohlsson et al. 2009; Tsai et al. 2010; Wen et al. 2011) and five medium-quality (Donohue et al. 2020; Lin S et al. 2011; Karampli et al. 2020; Murphy et al. 2018; Tobin et al. 2008) studies. Also, four high-quality studies suggested the adoption of new medicines by prescribers after approval was even greater if their peers were early adopters (Keating et al. 2020; Ohlsson et al. 2009; Tsai et al. 2010; Wen et al. 2011). Four medium-quality studies suggested peers from secondary care or specialist areas influenced primary care prescribers (Lin S et al. 2011; Karampli et al. 2020; Murphy et al. 2018; Tobin et al. 2008). Some prescribers stated that other colleagues, opinion leaders, and experts influenced the use of new medicines (Karampli et al. 2020; Lin S et al. 2011; Luo et al.
One high-quality study indicated peer influence being the greatest from month four of the medicine’s launch until month 17 (Manchanda et al. 2008). Another high-quality study observed that peer influence had a greater impact in the states of the USA with policies restricting pharmaceutical marketing (King and Bearman 2017).

Guidelines (n=6). Guidelines (local, national, or international) were indicated to influence prescribing decisions of some prescribers, especially of the less experienced (Karampli et al. 2020; Murphy et al. 2018; Netherland et al. 2009; Zhang et al. 2020). Some prescribers reported absence of guidelines prevented (Zhang et al. 2020) or delayed (Karampli et al. 2020) prescribing new medicines till a guideline was released. In one study some prescribers suggested difficulties in determining the position for the new medicine within a clinical pathway was a barrier for the uptake (Martin et al 2017). Contrastingly, one study reported the publication of national guidelines had no impact on the rate of uptake of the studied new medicine (Luo et al. 2018). All studies were medium quality.

Other information sources (n=6). Some prescribers in medium to high-quality studies reported conferences, medical or news articles, scientific societies’ websites, or clinical trial reports discussing new medicines having an impact on prescribing decisions (Chitagunta et al. 2009; Conti et al. 2012; Karampli et al. 2020; Murphy et al. 2018; Savage et al. 2012; Tobin et al. 2008). A high-quality study, looking at cyclooxygenase-2 inhibitors, suggested that medical articles discouraged prescribers to use new medicines, but news articles and media reports encouraged it (Chitagunta et al. 2009). Another high-quality study, looking at oral chemotherapy agents, observed that clinical trials and media reports published around the Food and Drug Administration (in the USA) approval date had a positive impact on the uptake (Conti et al. 2012). Some prescribers reported scientific literature having greater influence in prescribing decisions than information gathered through social professional networks (Karampli et al. 2020) or news media (Conti et al. 2012). Also, prescribers using national research websites were suggested to use new medicines earlier (Savage et al. 2012).

Organisation affiliations (n=6). Three studies indicated an organisation’s participation in research networks having a positive impact on new medicines use (Abraham et al. 2010; Karampli et al. 2020; Knudsen et al. 2009). This was attributed to an organisation’s experience with treatment protocols and exposure to the process of implementing new treatments. Also, organisational links with professional associations
were reported to increase the likelihood of being an early adopter in the case of buprenorphine (Savage et al. 2012). However, two studies suggested treatment programmes affiliated with medical health centres had the same or slower adoption rates than the independent ones (Keating et al. 2018; Freidman et al. 2010). All studies were medium quality.
### Table 2.5 Summary of factors affecting the uptake of new medicines referred to in the reviewed studies.

<table>
<thead>
<tr>
<th>Identified factor</th>
<th>Number of studies referred to the factor</th>
<th>As facilitator</th>
<th>As barrier</th>
<th>No impact</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (younger)</td>
<td>18</td>
<td>11</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>12</td>
<td>4</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Ethnicity (White)</td>
<td>10</td>
<td>6</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Education level (higher)</td>
<td>5</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Income (higher)</td>
<td>11</td>
<td>11</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Insurance (private or more comprehensive)</td>
<td>9</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residential area (urban or more affluent)</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health condition (more severe &amp; comorbidities)</td>
<td>13</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>9</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Patient satisfaction, adherence to current therapy &amp; monitoring</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response to current therapy (poor)</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient’s request &amp; therapy preferences</td>
<td>5</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prescriber factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (younger)</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>6</td>
<td>4</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Graduating from a top 20 medical or foreign school</td>
<td>3</td>
<td>3</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Principal or partner GP</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specialist or secondary care prescriber</td>
<td>16</td>
<td>13</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Non-academic prescriber</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greater prescribing volume or portfolio breadth</td>
<td>5</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knowledge of new medicine</td>
<td>7</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuing medical education activities</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>An early adopter in the past</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taking clinical risks &amp; spending less time in consultations</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medicine factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td>6</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety concerns (adverse &amp; long-term effects)</td>
<td>6</td>
<td></td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Interactions with food/medicines (less)</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High unit cost</td>
<td>5</td>
<td>5</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Therapeutic innovation</td>
<td>5</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ease of use &amp; administration</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Reduced monitoring &amp; clinic visits</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Organisational factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ownership status (private)</td>
<td>10</td>
<td>7</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Teaching status</td>
<td>8</td>
<td>1</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Size (larger)</td>
<td>17</td>
<td>11</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Location (more populated)</td>
<td>10</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Availability of supportive services</td>
<td>11</td>
<td>7</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Limited consultation time</td>
<td>2</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Number of specialists, nurses, or healthcare professionals (higher)</td>
<td>8</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Care co-ordination (fragmented)</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>External environment factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmaceutical detailing</td>
<td>11</td>
<td>11</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Formulary or reimbursement restrictions</td>
<td>10</td>
<td></td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Peer influence (internal &amp; external)</td>
<td>14</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommended by guideline (international, national, or local)</td>
<td>6</td>
<td>5</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Scientific literature, websites, &amp; conferences</td>
<td>6</td>
<td>6</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Organisational affiliations</td>
<td>6</td>
<td>4</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>
2.4 Discussion of key findings

This systematic review has identified a broad range of factors affecting the uptake of new medicines within healthcare organisations. The identified factors were grouped into patient, prescriber, medicine, organisation, and external environment factors as per Chaudoir et al. (2013) framework and overlapped with the Consolidated Framework for Implementation Research (CFIR) (Damschroder et al. 2009). The factors had a varied impact on the uptake of the different studied new medicines.

The findings of this review, which were different from earlier reviews (Chauhan and Mason 2008; Mason 2008; Lubloy 2014), indicated the presence of patient influence on the uptake of new medicines. Patients were reported to influence prescribing decisions through their interest in, or request for, new medicines, satisfaction with current treatment, and therapy preferences. However, only a small number of studies reported patient influence and further research is required to establish its relative importance in the uptake of new medicines. Also, reviewed studies did not explore the impact of patient involvement in decision-making, availability of patient choice, and the patient-clinician relationship, which are suggested to influence the implementation of health innovations (Chaudoir et al. 2013; Damschroder et al. 2009; Jaakkola et al. 2007). An understanding of these factors could offer an explanation for why new medicines are used with some patients types but not others.

In this review, high-quality studies indicated that patients with higher education levels were more likely to receive new medicines. This was in contrast to Lubloy’s review (2014) findings based on one study and not reported in the other two earlier reviews (Chauhan and Mason 2008; Mason 2008). Patient education level has been associated with health education, literacy, and behaviours (Hahn and Truman 2015), potentially translating into level of patient influence on new medicine use. Also, patient education level is linked with patient income (Godman et al. 2020). As in Lubloy’s review (2014), patients with higher income (able to pay out-of-pocket costs) and more comprehensive insurance plans were observed to have greater access to new medicines. This was more predominant in countries without universal health coverage, e.g. the USA, but was also present in countries with universal health coverage requiring co-payments from patients, e.g. Taiwan. More studies are needed to explore the impact of patient income on new medicine use in countries with publicly funded national health service, e.g. the UK.
Another important finding was the impact of new medicine cost to healthcare organisations and patients on its uptake. In contrast to previous reviews (Chauhan and Mason 2008; Mason 2008; Lubloy 2014), this review’s findings indicated that the high cost of a new medicine was a barrier for the uptake, although to a varied extent. Increasing costs and expenditure on medicines and limited available funding to healthcare services is anticipated to influence uptake of high-cost new medicines (Godman et al. 2020). Also, none of the reviewed studies considered the overall costs of new medicines compared to the established therapy (e.g. associated monitoring cost) or health economics (e.g. direct health costs), which could offer an explanation to observed geographical variation and restrictions of new medicine use in the reviewed studies.

This review’s findings also indicated that formulary or reimbursement restrictions influence the uptake of new medicines, which was not reported in earlier reviews (Chauhan and Mason 2008; Mason 2008; Lubloy 2014). The purpose of formulary and reimbursement restrictions is to ensure evidence-based and cost-effective prescribing. These could be used as a cost-control measure for high-cost new medicines limiting their use. Also, earlier reviews did not report the impact of guidelines (Lubloy et al. 2014) or concluded it had no (Mason 2008) or varied impact (Chauhan and Mason 2008). Our review findings suggest that guidelines have an impact on the uptake. Inclusion of new medicine in local or national guidelines establishes new medicines’ place in existing clinical pathways and provides assurance to prescribers that they follow the best practice.

Lastly, the review findings reaffirmed that prescribers’ experience and knowledge, peer influence, pharmaceutical detailing, staff composition at organisations, and scientific literature influence uptake of new medicines (Chauhan and Mason 2008; Mason 2008; Lubloy 2014). However, the present review also highlighted that studies reporting factors affecting new medicine use lacked exploration of the wider prescriber (e.g. motivation, values and goals, or beliefs about new medicines) and organisational (e.g. readiness for innovation, culture and climate, implementation process) factors reported in the implementation literature affecting the implementation of health innovations (Chaudoir et al. 2013; Damschroder et al. 2009; Nilsen 2015). Deficiency in reporting these factors could be due to the data sources used by the reviewed studies (mostly secondary administrative data from various databases) and lack of theoretical frameworks used to inform study designs of reviewed studies. Only 20 of the reviewed
studies referenced theoretical approaches employed but none of the studies addressed all constructs of the theoretical approach employed. Future studies employing determinant frameworks or implementation theories (Nilsen 2015) for primary data collection are required to address gaps in understanding barriers and facilitators to the implementation of new medicines into clinical practice.

2.5 Strengths and limitations

This systematic review had a broad search strategy over seven databases and included studies of all methodological designs, conducted in both primary and secondary care settings. Thus, it allowed a wide exploration of factors affecting the use of new medicines. Grey literature and non-English language articles were excluded for pragmatic reasons, so other relevant studies might have been missed. The synthesis was underpinned by a determinant framework used in implementation science, which allowed the conceptualisation of the findings as provided in the review. Most of the reviewed studies were medium (38 studies) or high-quality (26 studies) increasing confidence in the review findings. However, the QATSDD tool was critiqued to be subjective in nature as definitions of criteria were seen to be broad (Fenton et al. 2015). It was challenging to differentiate between scores for some criteria due to a lack of detail in definitions, which had led to different scores between reviewers. Also, some criteria seemed to be less applicable to certain study designs, for instance, user involvement and theoretical framework for secondary data analysis studies. Finally, included studies covered medicines with varied complexities and expertise required to prescribe them. Therefore, not all influential factors identified in the review are relevant to all healthcare settings and medicines, reducing the generalisability of the review findings.

2.6 Conclusions

This systematic review provides a comprehensive exploration of factors affecting the use of new medicines and identified potential gaps in the research literature, through the use of a determinant framework used in implementation science. Factors affecting new medicine use not reported in earlier reviews were identified and included patient influence and education level, cost of new medicines, formulary and reimbursement restrictions, and guidelines. Further research employing determinant frameworks or implementation theories are needed to address identified gaps, especially regarding a wider patient, prescriber, and organisational factors, in understanding barriers and facilitators to the uptake of new medicines into clinical practice.
Chapter 3 A narrative literature review of patients’ involvement in decision-making about oral anticoagulants for stroke prevention in non-valvular AF

3.1 Introduction

The systematic review described in the Chapter 2 highlighted the presence of patient influence on prescribing decisions through their interest in or request for new medicines, satisfaction with current treatment, and therapy preferences. However, only a small number of studies reported patient influence as most reviewed studies focused on patients’ demographic, socio-economic, and clinical characteristics. The reviewed studies did not explore the impact of patient involvement in decision-making, availability of patient choice, and patient-clinician relationship, which are suggested to influence implementation of health innovation (Chaudoir et al. 2013; Damschroder et al. 2009; Jaakkola et al. 2009). Also, healthcare systems have changed rapidly over the last ten years with an increasing focus on patient-centred care and patient involvement in decision-making (Loughlin et al. 2019), thus further research is required to explore patient influence on the use and uptake of new medicines.

A previous systematic meta-analysis (Xuereb et al. 2012) explored experiences of patients and clinicians about AF and oral anticoagulants. It also reported patients with AF involvement in decisions about oral anticoagulant therapy when vitamin K antagonists (mainly warfarin in the UK) were the only oral anticoagulant options available. Since 2012 four DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) became available as alternatives to vitamin K antagonists. Therefore, the previous systematic meta-analysis may not reflect the current picture of the involvement of this group of patients in the decision-making process. This narrative review aims to explore patient with AF involvement in decision-making when warfarin or warfarin with at least one DOAC were available, factors affecting patient involvement, and its impact on the use of DOACs.

3.2 Method

A systematised narrative literature review method, as defined by Grant and Booth (2009), was used. The literature review protocol, as per PROSPERO guidelines (Chien et al. 2012), was developed to minimise research bias and increase the robustness of the literature search (Centre for Reviews and Dissemination 2009). The PRISMA guidelines were followed (Moher et al. 2009). The literature review did not meet the full
criteria for a systematic review due to a single reviewer (KM) performing searches, data extraction, and quality appraisal.

3.2.1 Eligibility criteria

The inclusion criteria were established using the PICOS framework (population, interventions, comparators, outcomes, and study design) (Liberati et al. 2009). Three elements of the PICOS framework were relevant to this narrative literature review (population, outcomes, and study design). Each selection criteria with rationale are outlined below:

Inclusion criteria:

- Types of study: No restrictions to types of study were made to gain a better understanding of the subject. Therefore, qualitative, quantitative or mixed-methods empirical studies were eligible.
- Population: The prevalence of non-valvular AF is most common in older patients but can affect adults of any age (Public Health England 2017). Additionally, DOACs are not licensed in patients younger than 18 years old (Joint Formulary Committee 2019). Therefore, studies with adult participants (18 years and older) with non-valvular AF requiring or taking oral anticoagulants (a vitamin K antagonist (e.g. warfarin) or a DOAC) were eligible. Also, studies with healthcare professionals involved in the care of these patients were included.
- Outcome: Patients’ involvement in decision-making about oral anticoagulants for stroke prevention in non-valvular AF.
- Publication and language: Studies were not limited by date of publication, but language restrictions were applied. Only studies published in English were included due to financial and time constraints related to translation.

Exclusion criteria:

- Types of study: Grey literature (conference proceedings, posters, opinion pieces, Theses), review articles, clinical guidelines, and incomplete studies.
- Outcome: Studies only reporting patients’ preferences and perceptions of oral anticoagulants or focusing on decision aids for decision-making rather than reporting patients’ involvement in decision-making.

3.2.2 Search terms and information sources

Search terms were developed from three search categories: “atrial fibrillation”, “oral anticoagulant”, and “patient involvement”. The search terms were adapted to match
the keywords used in specific electronic databases. Seven electronic databases were searched: MEDLINE, EMBASE, Web of Science, CINAHL, Cochrane Library, SCOPUS, and PsychINFO. Each database was searched combining search terms with Boolean operators (AND/OR) and using truncation symbols for variant word endings and spelling. The full search strategy for the MEDLINE database is shown in Appendix B. Additionally, manual searches of citations and references of eligible studies and relevant systematic reviews were conducted to supplement database searches.

A subject librarian at the University of Bradford was consulted to ensure that the search strategy would identify relevant studies and the validity of the literature review. The search was initially completed on 3 August 2017 and then updated on 18 October 2018 and 3 April 2020. Reference management software (EndNote X7®) was used to organise and manage search results.

3.2.3 Selection of studies

After the removal of duplicate records using the reference management software, all retrieved titles followed by abstracts of remaining studies were screened using the inclusion and exclusion criteria. A second reviewer (DP) independently checked a random subset of 20% of retrieved titles and included abstracts to ensure concordance. The full text of potentially relevant studies was independently screened by two reviewers (KM and DP). Any disagreements in screening were discussed to reach a consensus. Once the screening was completed, reference lists and citations of included and relevant studies were screened using the eligibility criteria.

3.2.4 Data extraction

A data extraction form was developed using the guidelines for undertaking systematic reviews (Centre for Reviews and Dissemination 2009). It was piloted with five studies and then finalised. All included studies were read in-depth, and the following information was extracted using the data extraction form:

- Author, year, and country of publication;
- Aim(s) and/or objective(s) relevant to this literature review;
- Study design;
- Setting of the study;
- Included oral anticoagulants in the study;
- Data source;
- Data analysis method;
• Study participants’ details;
• Key findings relevant to this literature review.

3.2.5 Quality assessment

The QAT SDD tool validated to assess studies with heterogeneous study designs was used to assess the quality of included studies. The use of the QAT SDD tool is described in detail in Chapter 2 (see 2.2.5 Quality assessment). Studies were categorized as being of low (<50%), moderate (50% to <70.0%), or high (>70.0%) quality. Although the low methodological quality studies were not excluded, they were given less weight in the synthesis of results and conclusions.

3.2.6 Synthesis of results

A narrative synthesis of included studies aimed to represent the views of patients and prescribers on patient involvement in the decision-making process about oral anticoagulants for stroke prevention in non-valvular AF. The inductive thematic analysis approach by Braun and Clarke (2006) was followed for the analysis of review findings. Data synthesis and analysis consisted of six steps:

1. Familiarisation with the data by re-reading included studies and looking for patterns and meanings;
2. Creating initial codes from the findings of included studies;
3. Bringing initial codes together to identify preliminary themes and sub-themes;
4. Reviewing and refining preliminary themes and sub-themes to create potentially final themes and sub-themes;
5. Defining and naming themes to create final themes and sub-themes;
6. Writing a report explaining and discussing the identified themes and sub-themes.

The narrative synthesis results were discussed with the supervision team (DP, KS, SR).

Additionally, the findings were discussed with three members of the Patient and Public Involvement (PPI) advisory group to review the credibility of the findings. First, the literature review process was explained to the PPI advisory group. Then each group member was provided with a printed A4 poster (Appendix C) of the literature review abstract, which also detailed the developed themes and sub-themes. The researcher (KM) verbally summarised the findings and the group was asked to discuss if the findings reflected their experiences. They discussed how the results resonated with
their experience and if, in their view, any themes were missing. They also, rephrased some sub-themes to better reflect their meaning.

3.3 Results

3.3.1 Study selection

The selection process is summarised in the PRISMA flow-diagram in Figure 3.1. The search yielded 11,638 potential articles, and after the removal of duplicates, this was reduced to 8,655 unique titles. Screening of titles and abstracts resulted in 36 papers for further screening, and after a full-text review, 20 articles were excluded. Reasons for exclusion were: no findings on patient involvement in decision-making (n=14); development of a decision-aid tool (n=2); patients with other conditions than non-valvular AF (n=2); literature review (n=1); and not in English language (n=1). No additional studies were included after reference and citations screening. A total of 16 studies exploring patient involvement in decision-making about oral anticoagulants for stroke prevention in non-valvular AF were included in the narrative review. Out of 16 studies, three were also included in the Xuereb et al. (2012) meta-synthesis review.

3.3.2 Study characteristics

The characteristics of included studies are summarised in Table 3.1. Studies were published between 2004 and 2020, and four were conducted in the UK, three in Canada, two in the USA, one in Australia, Argentina, Denmark, Finland, Ireland, Romania, and one across multiple countries. Of the 16 studies, ten used qualitative and six quantitative methodologies. Study sample sizes ranged from 12 to 56 participants for qualitative studies and 53 to 444 for quantitative studies. Qualitative studies employed semi-structured face-to-face or telephone interviews, structured telephone interviews, observations, and online survey for data collection. Quantitative studies collected data using online, postal, or paper surveys.

Four qualitative studies explored patient involvement in decision-making when warfarin was the only oral anticoagulant option. Six qualitative and six quantitative studies were conducted when warfarin with at least one DOAC were available as therapy options. Seven studies reported only patients’ and six studies only prescribers’ perspectives. Three studies were conducted with both patients and prescribers.
3.3.3 Quality assessment

The methodological quality of studies ranged from 33% to 79%, with a mean score of 63% (Table 3.2). Two studies were deemed to be low, 10 medium, and four high quality. Table 3.3 summarises average scores for each of the 16 criteria used in the methodological quality assessment of included studies. Studies scored high for “statement of aims/objectives in the main body of report”, “clear description of research setting”, “fit between stated research question and method of data collection (quantitative only)”, “fit between stated research question and format and content of data collection tool (qualitative only)”, and “fit between research question and method
analysis”, scoring (mean score ± standard deviation) 2.82±0.40, 2.73±0.47, 2.40±0.55, 2.67±0.52, and 2.60±0.50 respectively. The lowest score (mean score ± standard deviation) of 0.09±0.30 was for “evidence of user involvement in design”. Only two of the included studies had some evidence of user involvement in design.
<table>
<thead>
<tr>
<th>Author(s), year, and country</th>
<th>Study objectives</th>
<th>Study design</th>
<th>Data source</th>
<th>Setting</th>
<th>Available therapy</th>
<th>Data analysis</th>
<th>Study participants</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aarnio et al. (2019), Finland</td>
<td>To understand how physicians choose an oral anticoagulant for patients with AF and view patients’ participation in the decision-making</td>
<td>Qualitative</td>
<td>Semi-structured face-to-face interviews</td>
<td>Primary and secondary care</td>
<td>Warfarin, DOACs</td>
<td>Thematic analysis</td>
<td>17 prescribers (8 GPs and 9 specialists)</td>
<td>• Patient’s preferences were the most influential factor in the decision-making when choosing between warfarin and a DOAC if no contraindications or other clinical factors were limiting the choice. • Patients’ views about the co-payment for oral anticoagulants, attitudes towards warfarin therapy monitoring, dosing, and antidote availability were considered. • In certain situations, some physicians limited the choice of oral anticoagulant or steered patients towards their preferred option.</td>
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<tr>
<td>Anderson et al. (2007), UK</td>
<td>To improve the understanding of physicians’ behaviour and attitudes in respect to decision-making in AF and the use of antithrombotics</td>
<td>Qualitative</td>
<td>Semi-structured interviews using clinical vignettes as a reference point</td>
<td>Secondary care</td>
<td>Warfarin</td>
<td>Grounded theory</td>
<td>14 hospital prescribers</td>
<td>• Decision-making in AF was associated with uncertainty and concerns about knowledge of risk and benefit. • Patients were viewed as a crucial part of the decision process, but there was a varied approach to the role of patients in decision-making.</td>
</tr>
<tr>
<td>Andrade et al. (2016), Canada</td>
<td>To assess the values, preferences, and experience of patients who receive oral anticoagulants therapy, and of physicians who prescribe them</td>
<td>Quantitative</td>
<td>Online survey</td>
<td>Primary and secondary care</td>
<td>Warfarin, DOACs (except edoxaban)</td>
<td>Statistical and descriptive analysis</td>
<td>266 patients 178 (GPs or specialists)</td>
<td>• Patients’ and physicians’ preferences differed but focused on safety and, to a lesser extent, efficacy. • 53% of physicians recommended only what they deemed the single most appropriate medication; 46 % provided several recommendations. • Among patients presented with several options, physicians reported that in 63% of cases, the final decision was made with their patient, in 15% by a physician, in 22% final decision was made by patients. • Among patients presented with several options, 46% of patients reported joint decision-making, 29% by prescriber alone, and 25% by patient. • In 56% of cases, a physician’s recommendation was the main reason for patients to switch to their current oral anticoagulants.</td>
</tr>
<tr>
<td>Author(s), year, and country</td>
<td>Study objectives</td>
<td>Study design</td>
<td>Data source</td>
<td>Setting</td>
<td>Available therapy</td>
<td>Data analysis</td>
<td>Study participants</td>
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</table>
| Baicus et al. (2019), Romania | To evaluate the shared decision-making process from the patients' perspective and identify patients' characteristics associated with the shared decision-making | Quantitative | Paper and online surveys | Secondary care | Warfarin, DOACs | Statistical and descriptive analysis | 235 patients | • Patients strongly or entirely agreed with all the Shared Decision-Making Questionnaire (SDM) statements, indicating shared decision-making.  
• Higher educational levels were associated with higher SDM scores |
| Choi et al. (2014), USA | To describe and compare characteristics of patients with AF who used dabigatran or only warfarin | Quantitative | Online survey | Primary care | Warfarin, dabigatran | Statistical analysis: descriptive, chi-squared, t-test | 364 patients | • Dabigatran users were more satisfied with their therapy and were more concerned about side effects and therapy costs than warfarin users.  
• Dabigatran users were more likely to discuss with the prescriber about their oral anticoagulant therapy options.  
• Warfarin users were more likely to leave the decision to the prescriber. |
| Clarke et al. (2017), UK | To explore the patient's lived experiences, perceptions of AF and anticoagulation, and the educational needs of AF patients taking dabigatran | Qualitative | Semi-structured interviews | Secondary care | Warfarin, dabigatran | Thematic analysis using essentialist/realist theoretical framework | 16 patients | • Warfarin-naïve patients viewed the decision as a means of survival rather than choice.  
• Warfarin-naïve patients used warfarin as a comparator when considering dabigatran.  
• Patients mentioned the need for guidance and implicit trust in the medical profession – "doctor knows best". |
| Dantas et al. (2004), Canada | To investigate the experiences and perspectives of individuals taking warfarin | Qualitative | Semi-structured face-to-face interviews | Primary care practice clinic within secondary care | Warfarin | Content analysis | 21 patients | • There was little or no patient involvement in the decision-making process.  
• Commencing warfarin during hospital admission precluded patients from any degree of significant participation in the decision-making. |
| Kirby et al. (2018), Ireland | To explore Irish GPs' experience of switching between oral anticoagulants for patients with AF and prevalence of multi-disciplinary decision making in switching decisions | Quantitative | Postal survey | Primary care | Warfarin, DOACs | Statistical analysis: probit regression model | 270 GPs | • There was a lack of patient involvement in the decision-making process when switching oral anticoagulants. They were involved only in 7% of the sample.  
• GPs in urban areas and GPs in training practices were more likely to involve patients. |
<table>
<thead>
<tr>
<th>Author(s), year, and country</th>
<th>Study objectives</th>
<th>Study design</th>
<th>Data source</th>
<th>Setting</th>
<th>Available therapy</th>
<th>Data analysis</th>
<th>Study participants</th>
<th>Key findings</th>
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</thead>
</table>
| Lipman et al. (2004), UK    | To explore how GPs with an active interest in research or evidence-based medicine make decisions about anticoagulation in patients with AF | Qualitative | Semi-structured interviews | Primary care | Warfarin | Framework analysis | 12 GPs | - The decision-making process was determined by interaction between GPs, hospital doctors, and patients and influenced by the evidence.  
- The role of the patient in the decision-making process was varied.  
- GPs influenced patients by a combination of persuasion, shared decision-making, GP- or patient-centred consulting, and explanation, with the GPs’ input being modified by their view of the evidence. |
| Pastore et al. (2019), Argentina | To evaluate the habits of anticoagulation initiation, difficulties in its continuity and the incorporation of DOACs | Quantitative | Online survey | Secondary care | Warfarin, DOACs | Statistical analysis: descriptive, chi-squared | 107 cardiologists | - 52.3% of respondents would explain the options to the patient and made the decision together.  
- 17.7% of respondents would start oral anticoagulants without involving the patient.  
- The results were independent of the institution type (public or private) and age of the prescriber. |
| Pokorney et al. (2019), USA | To explore decision-making by patients and physicians regarding oral anticoagulant use for stroke prevention in AF | Qualitative | Semi-structured telephone interviews | Primary and secondary care | Warfarin, DOACs | Content analysis | 28 physicians 25 patients | - Most patients preferred doctors to make the decision.  
- None of the patients experienced a shared decision-making conversation.  
- Patients preferred to learn about therapy options directly from doctors.  
- Physicians did not use decision aids.  
- Physicians found challenging in deciding what and how much information to communicate with patients. |
| Potpara et al. (2015), Europe | To explore the common practices in approaching patients with AF and informing them about their risk profiles and available therapies in Europe | Quantitative | Online survey | Secondary care | Warfarin, DOACs | Descriptive statistics | 53 responses from EHRA-EP research centres | - In 39% of centres information about DOACs was provided to all AF patients, in 42% to patients who were either warfarin-naive or unstable on warfarin, in 14% to patients unwilling to take vitamin K antagonists or in whom INR monitoring would be difficult, and in 3% to newly diagnosed AF patients.  
- When choosing a DOAC, in 79% of centres the decision was based on individual patient risk profile and national or international guidelines, in 17% based on prescriber’s clinical experience with a particular DOAC, in 2% based on DOACs availability in their hospital, and 2% based on the patient preference.  
- Patient preference-high relevance for oral anticoagulant therapy decisions in most centres. |
<table>
<thead>
<tr>
<th>Author(s), year, and country</th>
<th>Study objectives</th>
<th>Study design</th>
<th>Data source</th>
<th>Setting</th>
<th>Available therapy</th>
<th>Data analysis</th>
<th>Study participants</th>
<th>Key findings</th>
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</table>
| Salmasi et al. (2020), Canada | To describe AF patients’ experiences and perspectives of changes made to their oral anticoagulant therapy | Qualitative | Structured telephone interviews and online survey | Secondary care | Warfarin, DOACs | Thematic analysis and descriptive | 56 patients | Switches were physician or patient-initiated.  
Patients reported a lack of involvement in the decision-making about changing their oral anticoagulants.  
Some patients felt coerced and pressured into the therapy choice.  
Lack of shared decision-making often led to prescribing oral anticoagulants, which were not aligned with patients’ values and preferences. |
| Thrysoee et al. (2018), Denmark | To describe newly-referred AF patients’ experiences of the consultation process at an AF clinic. | Qualitative | Observations followed by semi-structured face-to-face interviews | Secondary care | Warfarin, DOACs | Phenomenological-hermeneutical approach | 14 patients | Patients found visiting the clinic was overwhelming; information was difficult to understand.  
Patients found it difficult to be involved in decision-making. |
| Wang and Bajorek (2016), Australia | To elicit emerging themes describing health professionals’ perspectives on the decision-making around antithrombotic therapy for stroke prevention in AF | Qualitative | Semi-structured face-to-face interviews | Primary and secondary care | Warfarin, DOACs | Thematic analysis | 26 prescribers (GPs, specialists, pharmacists, nurses) | Comprehensive assessments of patients are needed but not always implemented.  
Decision-making around antithrombotic is a negotiation between the prescribers’ preference and the patients’ preference.  
Health professionals from various disciplines focused on different aspects of the decision-making process. |
| Xuereb et al. (2016), UK | To understand participatory decision-making within the context of consultations about AF and warfarin | Qualitative | Semi-structured face-to-face interviews | Primary and secondary care | Warfarin | Interpretative phenomenological analysis | 12 patients 16 prescribers (specialists and GPs) | Patients reported a lack of choice and desire for choice in the treatment decision.  
Patients viewed consultations as didactic, not dialogic.  
Physicians in consultations navigated towards the ‘right’ decision.  
Physicians had a genuine aim for concordance, but it was overtaken by ingrained paternalism. |

AF-Atrial fibrillation; DOACs-Direct oral anticoagulants; GP-General Practitioner
### Table 3.2 The methodological quality of reviewed studies.

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## Table 3.3 Summary of the scores for the 16 criteria used to assess the methodological quality of the reviewed studies.

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<th>Standard deviation</th>
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<td>54%</td>
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<td>0.40</td>
<td>96%</td>
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<tr>
<td>3. Clear description of research setting</td>
<td>2.73</td>
<td>0.47</td>
<td>92%</td>
</tr>
<tr>
<td>4. Evidence of sample size considered in terms of analysis</td>
<td>2.64</td>
<td>0.81</td>
<td>71%</td>
</tr>
<tr>
<td>5. Representative sample of target group of a reasonable size</td>
<td>2.18</td>
<td>0.40</td>
<td>67%</td>
</tr>
<tr>
<td>6. Description of procedure for data collection</td>
<td>2.18</td>
<td>0.60</td>
<td>73%</td>
</tr>
<tr>
<td>7. Rationale for choice of data collection tool(s)</td>
<td>1.00</td>
<td>1.10</td>
<td>29%</td>
</tr>
<tr>
<td>8. Detailed recruitment data</td>
<td>2.36</td>
<td>0.81</td>
<td>67%</td>
</tr>
<tr>
<td>9. Statistical Assessment of reliability and validity of measurement tool(s) (Quantitative only)</td>
<td>0.80</td>
<td>1.30</td>
<td>22%</td>
</tr>
<tr>
<td>10. Fit between stated research question and method of data collection (Quantitative only)</td>
<td>2.40</td>
<td>0.55</td>
<td>83%</td>
</tr>
<tr>
<td>11. Fit between stated research question and format and content of data collection tool, e.g. interview schedule (Qualitative only)</td>
<td>2.67</td>
<td>0.52</td>
<td>87%</td>
</tr>
<tr>
<td>12. Fit between research question and method analysis</td>
<td>2.64</td>
<td>0.50</td>
<td>90%</td>
</tr>
<tr>
<td>13. Good justification for analytical method selected</td>
<td>1.36</td>
<td>1.29</td>
<td>40%</td>
</tr>
<tr>
<td>14. Assessment of reliability of analytical process (Qualitative only)</td>
<td>2.33</td>
<td>0.82</td>
<td>70%</td>
</tr>
<tr>
<td>15. Evidence of user involvement in design</td>
<td>0.09</td>
<td>0.30</td>
<td>6%</td>
</tr>
<tr>
<td>16. Strengths and limitations critically discussed</td>
<td>1.91</td>
<td>0.70</td>
<td>65%</td>
</tr>
</tbody>
</table>

### 3.3.4 Synthesis of results

Four themes, two from the patients’ and two from the prescribers’ perspective, were identified during the narrative synthesis. Table 3.4 presents the themes and sub-themes identified during the analysis and how sub-themes were refined after discussion with the supervision team and the PPI advisory group.
Table 3.4 Development of themes and sub-themes during the thematic analysis.

<table>
<thead>
<tr>
<th>Theme</th>
<th>Initial sub-theme</th>
<th>Final sub-theme</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients’ perspective</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient involvement in the decision-making</td>
<td>Doctors make decisions</td>
<td>Doctors make decisions for me</td>
</tr>
<tr>
<td></td>
<td>Passive role a) it should be this way b) active role denied</td>
<td>I am happy for doctor to make the decision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I wish to be involved in decision making</td>
</tr>
<tr>
<td></td>
<td>Active role (quantitative data)</td>
<td>I am involved in decisions</td>
</tr>
<tr>
<td><strong>Barriers for patient involvement</strong></td>
<td>Lack of information</td>
<td>I do not have enough information</td>
</tr>
<tr>
<td></td>
<td>Patients do not trust themselves</td>
<td>I do not trust myself to make the best decision</td>
</tr>
<tr>
<td></td>
<td>Setting: hospital, emergency</td>
<td>Environment (hospital, emergency)</td>
</tr>
<tr>
<td><strong>Prescribers’ perspectives</strong></td>
<td>Information provision by prescribers</td>
<td>Selective information</td>
</tr>
<tr>
<td></td>
<td>‘Right’ vs ‘wrong’ information</td>
<td>Assumption that patients collect incorrect information</td>
</tr>
<tr>
<td></td>
<td>Factors influencing what information is provided</td>
<td>Local protocols influence what information is provided</td>
</tr>
<tr>
<td><strong>Responsibility in decision-making</strong></td>
<td>It is not shared with patients</td>
<td>Decision is not shared with patients</td>
</tr>
<tr>
<td></td>
<td>Negotiation with patients</td>
<td>Decision is negotiated with patients</td>
</tr>
<tr>
<td></td>
<td>It is patient’s decision</td>
<td>It is patient’s decision</td>
</tr>
</tbody>
</table>

3.3.4.1 Patients’ perspective

Six qualitative studies (Clarkesmith et al. 2017; Dantas et al. 2004; Pokorney et al. 2019; Salmasi et al. 2020; Thrysoee et al. 2018; Xuereb et al. 2016) and three quantitative studies (Andrade et al. 2017; Baicus et al. 2019; Choi et al. 2014) reported patients’ perspectives on their involvement in the decision-making process about oral anticoagulants for stroke prevention in non-valvular AF. All studies were medium to high quality. Two main themes were identified: patient involvement in the decision-making and barriers to patient involvement.
Patient involvement in the decision-making

Patients largely viewed that doctors were making decisions regarding oral anticoagulant therapy for stroke prevention in non-valvular AF. This was present in studies conducted both when warfarin (Dantas et al. 2004; Xuereb et al. 2016) and warfarin with at least one DOAC (Andrade et al. 2017; Choi et al. 2014; Clarkesmith et al. 2017; Pokorney et al. 2019; Salmasi et al. 2020; Thrysoee et al. 2018) were available as therapy choices. Patients felt that they took what they were told without being included in the decision-making process (Clarkesmith et al. 2017; Dantas et al. 2004; Pokorney et al. 2019; Salmasi et al. 2020; Thrysoee et al. 2018; Xuereb et al. 2016). Also, patients reported little or no involvement when oral anticoagulants were switched, e.g. warfarin to a DOAC (Salmasi et al. 2020).

Some patients viewed that doctors making decisions was the way it should be as “doctor knows best” and were seen to be experts (Clarkesmith et al. 2017; Pokorney et al. 2019; Salmasi et al. 2020; Xuereb et al. 2016). These patients accepted their passive role in the decision-making process and deferred the decision-making responsibility to the prescriber. They expressed high trust in doctors and their recommendations and did not question their lack of involvement in the process.

Although some patients preferred a paternalistic approach (clinician making a decision based on patient’s clinical picture without patient involvement), other patients wanted to have a more active role in the decision-making process (Salmasi et al. 2020; Xuereb et al. 2016). They expressed that their preferences and opinions were important to consider but were not addressed as consultations were prescriber-centred (Clarkesmith et al. 2017; Salmasi et al. 2020; Xuereb et al. 2016). These patients wanted to have some control of the decision-making process but were not enabled to do so. Lack of involvement for these patients caused dissatisfaction with the consultation (Salmasi et al. 2020; Xuereb et al. 2016), led to not taking the prescribed oral anticoagulant (Salmasi et al. 2020), or even questioning the ulterior motives and knowledge of the prescriber (Salmasi et al. 2020).

Patients reported making decisions together with prescribers or themselves only in quantitative studies conducted when warfarin with at least one DOAC were available as therapy choices (Andrade et al. 2017; Baicus et al. 2019; Choi et al. 2014). Although the paternalistic consultation approach was still present, patients reported involvement in the decision-making when presented with several therapy choices (Andrade et al. 2017; Choi et al. 2014). One study, using a survey, observed that in such cases, almost
half of decisions were made together with prescribers and in one-quarter of cases were made solely by the patient (Andrade et al. 2017). Notably, patients initiated on a DOAC rather than warfarin were more likely to be involved in the decision-making process (Choi et al. 2014). Baicus et al. (2019) study used a validated shared decision-making questionnaire, and patients, particularly with higher educational levels, scored high for each criterion, indicating their involvement in the decision-making process. However, the questionnaire was not anonymous, which may have prevented patients to report their true experience.

Barriers to patient involvement

Qualitative analysis of patient narratives highlighted several barriers to their active participation in the decision-making process. Patients did not trust themselves to make decisions, which stemmed from lack of knowledge needed to make the decision (Clarkesmith et al. 2017; Dantas et al. 2004; Thrysoee et al. 2018; Xuereb et al. 2016), a perception that they had no choice as the therapy was crucial for their survival (Clarkesmith et al. 2017; Dantas et al. 2004; Pokorney et al. 2019), or it was prescribers’ job to make the decision (Clarkesmith et al. 2017; Dantas et al. 2004; Pokorney et al. 2019; Pokorney et al. 2019; Salmasi et al. 2020; Xuereb et al. 2016).

In the studies reviewed, patients viewed prescribers as well-informed experts and thus relied on them not only for information provision but also for guidance (Clarkesmith et al. 2017; Dantas et al. 2004; Pokorney et al. 2019; Thrysoee et al. 2018; Xuereb et al. 2016). Some patients viewed didactic consultations as a necessity due to the complexity of the condition and unarguable need for treatment for survival (Clarkesmith et al. 2017; Dantas et al. 2004; Pokorney et al. 2019). The lack of knowledge and fear of adverse outcomes deterred them from the idea of active involvement in the decision-making process. Therefore, they accepted the role of a listener and deferred the decision-making responsibility to the prescriber.

A hospital setting was also identified as a barrier to being involved in decision-making (Dantas et al. 2004). Patients who were started on an oral anticoagulant during hospital admission were not included in the decision-making process. They learned about the started oral anticoagulant therapy after the decision was made (e.g. during the discharge process). Additionally, the short length of outpatient consultations limited discussions about available therapy choices and thus chances of patients being involved in the decision-making process (Thrysoee et al. 2018; Xuereb et al. 2016).
3.3.4.2 Prescribers' perspective

Six qualitative studies (Aarnio et al. 2019; Anderson et al. 2007; Lipman et al. 2004; Pokorney et al. 2019; Wang and Bajorek 2016; Xuereb et al. 2016) and four quantitative studies (Andrade et al. 2017; Kirby et al. 2018; Pastore et al. 2019; Potpara et al. 2015) explored perspectives of prescribers on patient involvement in the decision-making about oral anticoagulants for stroke prevention in non-valvular AF. Studies were low to high quality. Two themes were identified: information provision by prescribers for the decision-making and responsibility share in the decision-making.

Information provision by prescribers

Prescribers recognised that patients depended on their expertise and providing patients with verbal and written information equipped them to participate in the decision-making process (Anderson et al. 2007; Lipman et al. 2004; Pastore et al. 2019; Wang and Bajorek 2016; Xuereb et al. 2016). The source of information was important too. Prescribers viewed information obtained from them to be the “right” information. In contrast, knowledge acquired by patients from other sources tended to be assumed to be inaccurate, which could have led patients into making “wrong” decisions (Xuereb et al. 2016). Equally, patients trusted the information obtained from doctors and preferred learning about therapy options directly from them (Pokorney et al. 2019).

Some prescribers encouraged patients to make the decision after providing them with the information (written, verbal, or both) required to make the decision (Anderson et al. 2007; Lipman et al. 2004; Xuereb et al. 2016). However, prescribers found the decision on what and how much information to provide to their patients challenging (Pokorney et al. 2019). There was a tension between the “right” decision perceived by the prescriber and the patient’s personal choice (Lipman et al. 2004; Xuereb et al. 2016). In order to reach the “right” decision, patients were steered into decisions with the provision of selective information, e.g. leaving out negative information (Xuereb et al. 2016) or limiting information about available therapy choices (Aarnio et al. 2019; Andrade et al. 2017; Potpara et al. 2015). A survey study showed that half of the prescribers told patients only about one therapy option, which was deemed the “right” one by the prescriber (Andrade et al. 2017). Additionally, the fear of stroke was used in consultations to steer patients towards the decision preferred by the prescriber (Xuereb et al. 2016). Selective information led patients to make or accept decisions
that were preferred by the prescriber but did not necessarily address patients’ preferences, expectations, and concerns (Salmasi et al. 2020; Xuereb et al. 2016).

The need to provide selective information could come not only from a prescriber’s view of what was the “right” decision but might had been influenced by local protocols in health care organisations. A survey of European electrophysiology centres revealed that information about DOACs was not presented to all patients requiring oral anticoagulant therapy, but it was a low-quality study. In some centres, information about DOACs was limited to specific groups of patients, e.g. warfarin-naïve or unstable on warfarin, patients unwilling to take warfarin or to undertake necessary monitoring, or newly diagnosed patients with AF (Potpara et al. 2015).

Share of responsibility in decision-making

Prescribers are in a position to enable patients to be involved in decisions and share with or pass the decision-making responsibility to patients. Narratives from qualitative studies (Aarnio et al. 2019; Anderson et al. 2007; Lipman et al. 2004; Wang and Bajorek 2016; Xuereb et al. 2016) and results from quantitative surveys (Pastore et al. 2019) demonstrated prescribers’ desire to involve patients in the decision-making process. Patients’ preferences, opinions, and concerns were seen as important aspects to consider when starting oral anticoagulation therapy (Aarnio et al. 2019; Anderson et al. 2007; Lipman et al. 2004; Potpara et al. 2015) or switching between oral anticoagulants (Aarnio et al. 2019). Some prescribers perceived the decision-making as a negotiation with the patient (Andrade et al. 2017; Lipman et al. 2004; Pastore et al. 2019; Wang and Bajorek 2016) leading to sharing the responsibility of the decision-making. Other prescribers took it further and enabled patients to make the final decision (Anderson et al. 2007; Andrade et al. 2017; Lipman et al. 2004) and hence transferred the decision-making responsibility to patients. High uncertainty regarding the “right” decision also stimulated greater patient involvement in the decision-making process (Anderson et al. 2007). However, persuasion or limiting therapy options were also reported in consultations to steer the patient towards a prescriber’s preferred option (Aarnio et al. 2019; Lipman et al. 2004; Salmasi et al. 2020; Wang and Bajorek 2016; Xuereb et al. 2016) and thus lessening the role of patients in the decision-making.

Although the importance of patient involvement in the decision-making was recognised, in some cases prescribers fell back to the paternalistic approach (Lipman et al. 2004; Xuereb et al. 2016). The paternalistic consultation approach resulted from
prescribers' view that patients would make a “wrong” decision (Xuereb et al. 2016), an insufficient time within the consultations to allow for a shared decision-making consultation (Xuereb et al. 2016), hospital setting (Lipman et al. 2004), not using patient decision aids (Pokorney et al. 2019), and patients deferring the decision-making responsibility to prescribers (Pokorney et al. 2019; Xuereb et al. 2016). As a result, in these cases, the decision-making responsibility stayed with prescribers.

Some prescribers did not attempt to involve patients in the process and made the decision themselves despite more than one therapy choice available (Kirby et al. 2018; Pastore et al. 2019). Kirby et al. (2018) observed that general practitioners predominantly did not involve patients in the decision-making process when switching oral anticoagulants in a general practice setting. If a patient was involved, it was only when more than one clinician was involved in the care of the patient (e.g. hospital clinician and GP) and more likely to occur with general practitioners in training or urban areas practices.

3.4 Discussion

The literature review has identified 16 studies of varying quality exploring patient involvement in the decision-making about oral anticoagulants for stroke prevention in non-valvular AF. In line with the Xuereb et al. (2012) meta-synthesis, this review highlighted that patients had no or limited involvement in decision-making and therapy decision were predominantly made by clinicians. Inclusion of studies when warfarin with at least one DOAC were available as therapy options in this review highlighted the emergence of patient involvement in the decision-making process from both patients' and prescribers' perspectives.

The reviewed literature showed that patients wanted different levels of involvement (passive role - paternalistic, shared decision, or autonomous role) in the decision-making process, which was not always identified and facilitated. This observation was not unique to patients with AF as patient preferences for involvement in the treatment decision-making has been shown to vary in other conditions too (Chewning et al. 2012; Levinson et al. 2005; Mah et al. 2016; Mazur and Hickam 1997). However, the preference for the passive role may result from a lack of knowledge, as highlighted in this literature review, leading to patients not trusting themselves to make treatment decisions and not seeking an active role in the decision-making process. It has been shown that patients, regardless of their preference for involvement, want to be told about available therapy choices (Mah et al. 2016) and associated risks with available
treatment (Mazur and Hickam 1997). Providing information about available therapy options can stimulate patients to take a more active rather than passive role in the decision-making, which will likely be due to them being better informed and more knowledgeable (Stacey et al. 2017).

This review indicated that patients were provided with selective information, potentially influenced by prescribers’ views, to steer them towards the prescribers’ or organisations’ preferred therapy option. It could have a negative impact on DOAC use if warfarin was the preferred option. Also, the use of selective information in consultations could limit patients’ involvement in decision-making and lead to failure in recognising patients’ treatment preferences. Acknowledging patients’ preferences is thought to improve patients’ satisfaction with the consultation, which in turn may lead to adherence to the prescribed therapy and overall health (Shay and Lafata 2015).

Both patients and prescribers identified that time allocated for a consultation could be one of the barriers to active patient involvement in the decision-making. The short length of consultations, often under 10 minutes in the UK, has been shown to be associated with poor communication with patients (Irving et al. 2017). The communication with patients could be improved by using patient decision aids (Stacey et al. 2017a) that were shown to have no or little impact on prolonging the consultation (Stacey et al. 2017b). Patient decision aids support discussion between patient and prescriber around benefits and harms of available therapy choices and establish patient preferences (O’Neill et al. 2017; Stacey et al. 2017a). Their use was shown to improve patient knowledge about available therapy options, increased patient involvement in the decision-making process, and prescribing a therapy that matches patients’ values and preferences (Loewen et al. 2019; O’Neill et al. 2017; Stacey et al. 2017a). In the reviewed studies, the use, more accurately, the lack of use of patient decision-aids was discussed only in Pokorney et al. (2019) study. Also, the format of the information presented was shown to be important as patients understood better pictorial rather than verbal information (Fuller et al. 2004; Katz et al. 2006). Also, a combination of different formats (written, verbal, pictorial) was suggested to improve patient’s understanding and adherence to therapy (Fuller et al. 2004; Katz et al. 2006).

Additionally, patients identified a hospital setting as a barrier to being involved in the decision-making process. Although reviewed studies did not explore why Dyrstad et al. (2015) study with healthcare professionals in the emergency department suggested that restraints on resources and healthcare professionals’ attitudes were factors
leading to the lack of patient involvement in the decision-making during hospital stays. Meeting patients’ physical needs is a priority for prescribers during hospital admission. Consequently, this can result in little or no patient involvement in the decision-making as procedure and symptom orientated care is prioritised (Dyrstad et al. 2015). However, patients could be offered an opportunity to review and change therapy based on their preferences after discharge.

Patient involvement in decision-making is challenging in practice, but it can improve patients’ confidence in managing their health (Loughlin et al. 2019). Prescribers are well-positioned to engage and empower patients to move from passive to a more active role in the decision-making process. This can be achieved by establishing patients’ preference for involvement, providing information on available therapy options, establishing what is important to patients and their preferences, and respect their decision (which may or may not differ from the prescribers’ preferred choice) (Chewning et al. 2012; Elwyn et al. 2012; Loughlin et al. 2019).

It is difficult to determine from the reviewed literature if additional oral anticoagulant options (i.e., the availability of DOACs as well as coumarins) for stroke prevention in non-valvular AF had an impact on patients’ level of involvement in the decision-making. Nevertheless, the notion of patients feeling that decisions were shared or made by them emerged only from studies when warfarin with at least one DOAC were available. In the United Kingdom (UK) context, only one study was conducted when warfarin with one DOAC, dabigatran, were available as therapy choices (Clarkesmith et al. 2017). However, this may not reflect the current practice as rivaroxaban, apixaban, and edoxaban are now also available in the UK, and the use of dabigatran is minimal (Loo et al. 2017). Also, patients reported their involvement only in quantitative surveys, whereas prescribers indicated a desire to engage patients in decisions in both qualitative and quantitative studies. More qualitative research with patients is required to determine if patients experience involvement in the decision-making process since several oral anticoagulant therapy options are available.

3.5 Strengths and limitations

The narrative literature review has several strengths. Although it is not classed as a systematic review, a systematic approach of reporting was followed (Moher et al. 2009) and a validated quality appraisal tool was used (Sirriyeh et al. 2012) to increase the quality and robustness of the review (Centre for Reviews and Dissemination 2009). Additionally, the developed search strategy was discussed with the information
specialist at the University of Bradford, and a range of databases was used to conduct searches. Furthermore, the findings were discussed with and validated by the PPI advisory group to minimise one reviewer’s subjective bias.

Several steps of the review (data extraction, quality assessment of studies, narrative synthesis) were performed without an additional independent reviewer, which might have introduced the reviewer’s bias. Secondly, non-English language studies were excluded due to practical reasons (limited time and budget). This might have limited the number of final studies included in the review.

3.6 Conclusions

The studies reviewed described patients with non-valvular AF involvement in the decision-making about oral anticoagulant therapy. Patient and prescriber reports suggested that there was a desire to engage patients in the decision-making process, mainly when several therapy options were available. Patient involvement (or lack of) and provision of information about therapy options could potentially influence the use of DOACs and hence their uptake. This requires further exploration, and qualitative interviews with this group of patients will be undertaken to explore patients’ roles in the uptake of DOACs and factors affecting the use of DOACs from their perspective.

The following chapter will describe the methodology employed to explore factors affecting the uptake of DOACs from the perspectives of patients, healthcare professionals, and identified key stakeholders.
Chapter 4 Methodology

4.1 Overview

This chapter outlines the rationale for the research methodology adopted, the philosophical underpinnings informing the research, methods used, and discusses ethical considerations. The study employed a qualitative research approach underpinned by a critical realism philosophical framework and informed by the Diffusion of Innovations in Service Organisations model. Although the study described in this thesis is underpinned by a critical realism philosophical framework, it is not associated with any specific research method (Fletcher 2017; Mingers 2004). Thus, permitting the researcher to select research methods that would allow the best understanding and explanation of factors affecting the uptake of DOACs within the three different health economies. In line with a qualitative inquiry, non-participant observations and semi-structured interviews were used to collect the data. The collected data were analysed using the Framework Analysis method (Ritchie et al. 2014). The overall research described in this thesis consisted of four phases (Figure 4.1):

1 Review of the literature to inform development of research questions and design of the research study described in this thesis.
   1a - A systematic literature review to identify reported barriers and enablers to the uptake of new medicines. It was reported in Chapter 2.
   1b - A systematised narrative literature review to explore the role of patients in the uptake of DOACs. It was reported in Chapter 3.

2 Non-participant observations of meetings and collection of documents to understand the process of new medicines implementation within studied health economies. Information from meetings was used to identified participants for Phase 3 and inform the semi-structured interviews.

3 Semi-structured interviews with patients, healthcare professionals, and identified key stakeholders to explore barriers and enablers to the uptake of DOACs.
   3a - Semi-structured interviews with patients taking oral anticoagulants for stroke prevention in non-valvular AF. Interviews explored the roles of patients
in the uptake of DOACs and factors affecting the use of DOACs from their perspective. The findings are reported in Chapter 5.

3b - Semi-structured interviews with healthcare professionals involved in the care of patients with non-valvular AF. Interviews explored views of healthcare professionals on barriers and enablers to the uptake of DOACs within the studied health economies. The findings are reported in Chapter 6.

3c - Semi-structured interviews with identified key stakeholders (other than patients and healthcare professionals) involved in the implementation of DOACs within the studied health economies. Interviews explored views of key stakeholders on barriers and enablers to the uptake of DOACs within the studied health economies. The findings are reported in Chapter 6.

4 Development of potential components of a toolkit for use in clinical practice to address the identified barriers to the uptake of new medicines. The findings are reported in Chapter 7.
Figure 4.1 Summary of the research study described in this thesis.
4.2 Study settings

The research study was undertaken in three health economies in the North of England. Population and health outcomes of the studied health economies are described using information from Public Health England Health Profiles (Public Health England 2018). Prescribing trends of DOACs are described using data from Open Prescribing (OpenPrescribing.net 2019). It should be noted that the prescribing data of oral anticoagulants include all indications, however, oral anticoagulants are predominantly used for stroke prevention in AF. The non-AF indications (e.g. venous thromboembolism, antiphospholipid syndrome) have a much lower prevalence compared to AF (Orlowski et al. 2021). The Table 4.1 summarises the key characteristics of the studied health economies.

These health economies were selected due to different levels of DOACs uptake and having different mechanisms for approval and support of entry of new medicines into practice. Thus, investigating health economies with different medicines management processes could provide richer insights into the barriers and enablers to the local uptake of DOACs. The results could also be more likely to have resonance with experiences in other health economies in England.

Table 4.1 Key characteristics of the studied three health economies.

<table>
<thead>
<tr>
<th>Key characteristics</th>
<th>Health Economy A</th>
<th>Health Economy B</th>
<th>Health Economy C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of CCGs</td>
<td>Two (City and District)</td>
<td>Three (A,B,C)</td>
<td>One</td>
</tr>
<tr>
<td>Population</td>
<td>Around 450,000</td>
<td>Around 870,000</td>
<td>Around 580,000</td>
</tr>
<tr>
<td>Mortality rate (deaths per 100,000) from cardiovascular diseases in 2016-2018</td>
<td>105</td>
<td>86.3</td>
<td>82.7</td>
</tr>
<tr>
<td>Prevalence of AF in 2017-2018</td>
<td>City CCG: 0.5% District CCG: 1.7%</td>
<td>A &amp; B CCGs: 1.7% C CCG:1.5%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Prevalence of stroke in 2017-2018</td>
<td>City CCG: 0.9% District CCG: 1.8%</td>
<td>A CCG: 1.7% B CCG: 1.8% C CCG: 1.5%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Proportion of DOAC versus warfarin use</td>
<td>22% in August 2014 73% in August 2019</td>
<td>3% in August 2014 51% in August 2019</td>
<td>15% in August 2014 70% in August 2019</td>
</tr>
<tr>
<td>Anticoagulation service set-up</td>
<td>Any qualified provider</td>
<td>A single provider (secondary care)</td>
<td>Any qualified provider</td>
</tr>
</tbody>
</table>
4.2.1 Health economy A

Health economy A consisted of two CCGs, City and Districts. City CCG served a population of almost 120,000 whereas Districts CCG of 330,000 people. The mortality rate from cardiovascular diseases, including stroke, in people under 75 years of age was higher than the national average in England. In 2016-2018 it was 105 deaths per 100,000 compared to 71.7 in England. It meant that the health economy A was in the worst to 25th percentile category.

The prevalence of AF in 2017-2018 differed between the two CCGs, 0.5% in City CCG and 1.7% in Districts CCG, and was lower than the national average of 1.9% in England. The prevalence of stroke in 2017-2018 was 0.9% and 1.8% in City CCG and Districts CCG respectively, whereas the national average in England was 1.8%.

The proportion of DOAC versus warfarin use increased from 22% in August 2014 to 73% in August 2019. In both CCGs, it was higher than the national average in England, which was 9% in August 2014 and 63% in August 2019.

The anticoagulation services were provided by any qualified provider in both primary (general practice) or secondary (local hospital trust) care. The commissioned service was explicitly designed for monitoring of warfarin therapy and also included initiation, dosing, dose adjustments, and provision of the patient-facing elements of the service. The warfarin clinics occurred across a range of locations, including community pharmacy clinics, general practices, or secondary care clinics. Patients were offered a choice of the anticoagulation clinic and referred to the service by clinicians or GPs (paper or electronic referral). Whereas initiation and prescribing of DOACs, together with any future review of the patients care plan, was conducted outside the anticoagulation service. Warfarin and DOACs could have been prescribed by primary or secondary care for licensed indications.

4.2.2 Health economy B

Health economy B consisted of three NHS CCGs. All three CCGs combined served a population of around 870,000 people. The mortality rate from cardiovascular diseases, including stroke, in people under 75 years of age was higher than the national average in England. In 2016-2018 it was 86.3 deaths per 100,000 compared to 71.7 in England. It meant that the health economy B was in the “25th to 75th percentile” category.
The prevalence of AF in 2017-2018 in two CCGs was 1.7% and in the third 1.5%; lower than the national average of 1.9% in England. The prevalence of stroke in 2017-2018 was 1.7%, 1.8% and 1.5% in the three CCGs. It was lower or the same as the national average prevalence of 1.8% in England.

The proportion of DOAC versus warfarin use increased from 3% in August 2014 to 51% in August 2019. It was lower than the national average in England, which was 9% in August 2014 and 63% in August 2019.

The anticoagulation services were provided by a single provider, which was an acute trust (secondary care). Clinicians and GPs identified patients with AF and referred them to the service where patients were offered a choice of therapy and started on anticoagulation. The provider delivered all elements associated with prescribing including initiation, dosing, dose adjustment, and laboratory testing as well as undertaking monitoring and providing the patient-facing elements of the service. All patient information was maintained on a single clinical records system which was separate from the patient's general practice record. The anticoagulation service had warfarin and DOAC clinics. DOACs were reserved for patients with poor warfarin monitoring results. As the service was provided by secondary care, initiation of both warfarin and DOACs was reserved to the hospital and GPs continued the prescribed therapy.

4.2.3 Health economy C

Health economy C consisted of one NHS CCG and served a population of around 580,000 people. The mortality rate from cardiovascular diseases, including stroke, in people under 75 years of age was higher than the national average in England. In 2016-2018 it was 82.7 deaths per 100,000 compared to 71.7 in England. It meant that the health economy C was in the "25th to 75th percentile" category.

The prevalence of AF in 2017-2018 was 2.0%; higher than the national average of 1.9% in England. The prevalence of stroke in 2017-2018 was 2.0%; higher than the national average of 1.8% in England.

The proportion of DOAC versus warfarin use increased from 15% in August 2014 to 70% in August 2019. It was higher than the national average in England, which was 9% in August 2014 and 63% in August 2019.
The anticoagulation services are provided by any qualified provider, primary (general practices) or secondary care (local hospital Trust) but generally on a shared care basis. Although GPs, contracted to provide anticoagulation service, could initiate warfarin, warfarin was generally initiated at the secondary care anticoagulation clinic. GPs did the ongoing warfarin prescribing. Continuous monitoring of warfarin therapy was undertaken in the secondary care anticoagulation clinic, or patients were transferred to warfarin clinics in primary care (community pharmacy or general practices clinics). Whereas DOACs could be initiated by both primary and secondary care and ongoing monitoring with follow-up were undertaken by GPs.

4.2.4 Uptake of DOACs for AF

During the introduction of DOACs, various national campaigns and changes to national health directives and policies occurred, which may have influenced local uptake of DOACs (Figure 4.2). The local DOAC uptake data specifically for patients with AF was obtained for A and B health economies during the research design stage (Figure 4.3). The data for health economy C was requested but was not available for public use. In health economy A, the uptake of DOACs was relatively faster and higher than in health economy B. DOAC use was similar to warfarin use by early 2017, 49% versus 51%. Contrastingly, in the health economy B warfarin continued to be a predominant oral anticoagulant. By early 2017, DOACs comprised 11% of all oral anticoagulant prescribing for AF patients, well below the expected national uptake level of 35%. Notably, one year after the NICE AF management guideline update (NICE 2014b) DOAC therapy was prescribed to only 7% of patients diagnosed with AF and eligible for anticoagulation therapy. Furthermore, approximately between 1/3 to 1/4 of patients in both areas have received ineffective (aspirin) or no therapy at all, in line with the UK figures described earlier. The highly variable local DOAC uptake demonstrates the importance of investigating factors affecting the DOAC uptake potentially leading to inequality of AF patient care across England.
Figure 4.2 Timeline of key national events and changes to national and international guidelines. AF - atrial fibrillation; DOACs - direct oral anticoagulants; ESC - European Society of Cardiology; NICE - National Institute for Health and Care Excellence; QOF - Quality Outcome Framework for general practice; TA - technology appraisal by NICE.
Figure 4.3 The DOAC uptake for AF in health economies A and B between July 2015 and January 2017. Graphs 1 and 3 show oral anticoagulant and antiplatelet prescribing in patients diagnosed with AF and eligible for anticoagulation therapy. Graphs 2 and 4 indicate DOAC use versus warfarin. Data source: local medicine optimisation dashboards (unpublished).
4.3 Philosophical assumptions

The philosophical assumptions of a researcher are important as they shape and inform the design and conduct of a research study (Creswell 2013; Crotty 1998). Creswell (2013) argues that there are four philosophical assumptions to be considered: ontological (nature of the reality), epistemological (how reality is known), axiological (role of values), and methodological (the process of research). Philosophical assumptions underlining the study described in this thesis align with the critical realism philosophical framework.

4.3.1 Ontological assumption

Ontological assumptions refer to beliefs held by the researcher about the nature of reality or what exists (Creswell 2013; Edwards et al. 2015). These ontological assumptions differ between different philosophical frameworks.

Positivism holds the view that there is a single reality that can be observed and is independent of researchers (Creswell 2013; Edwards et al. 2015; Mingers 2004). Positivists believe that only observable and measurable things are real. As a result, positivism informed research focuses on objective empirical observations in a closed system to test the pre-determined hypothesis and generate universally applicable laws through experimentation (Edwards et al. 2015; Mingers 2004). Positivism is mostly employed in quantitative research.

At the other end of the spectrum, social constructivism argues there is no single reality but multiple realities. These realities are socially constructed by individuals through their interactions with the world and lived experiences. Researchers aim to explore these multiple realities and acknowledge a subjective nature of them (Creswell 2013). This philosophical stance is frequently employed in qualitative research.

The study described in this thesis takes critical realism ontological assumptions. Critical realism includes elements from both positivism and social constructivism (Edwards et al. 2015; Fletcher 2017). Critical realism acknowledges and critiques both positivism’s and social constructivism’s ontological assumptions (Alvesson and Skoldberg 2009; Edwards et al. 2015; Mingers 2004). Critical realists believe in an objective reality as positivists do. However, they also recognise that this reality is open to subjective interpretations and influences from a broader context within the studied social phenomenon (Edwards et al. 2015). They criticise positivists for focusing only
on describing empirical events by providing numbers and testing relationships between tested variables. Thus, failing to recognise the broader context of influences that may not be observable but generate the observed events (Edwards et al. 2015; Mingers 2004).

Most of the studies reviewed in the systematic review (Chapter 2) were quantitative studies employing a positivist philosophical view. These studies identified relationships between tested variables, e.g. specialists are more likely to prescribe new medicines. However, they did not explore the underlining causes of the observed relationships. Thus, failing to provide an in depth understanding of factors affecting the use of new medicines.

A more in depth understanding of factors affecting the use of new medicines with an exploration of underlying causal mechanisms can be provided by social constructivism inquiry. Critical realists, as constructivist acknowledge, believe there is a reality that cannot be observed or measured that influences and generates events we observe (Edwards et al. 2015; Mingers 2004). However, social constructivism believes reality is only what we experience. Social constructivism also rejects the non-subjective reality that can provide a more accurate description of reality. Whereas critical realists are equipped to acknowledge and distinguish between the reality as experienced by individuals and more universal reality.

As a result, critical realism acknowledges both natural and social sciences, and its ontological assumptions are stratified with three overlapping reality domains: empirical, actual, and real. The actual reality domain refers to all events that occur, both observed or experienced, and not. These events are independent of our perceptions of them. A subset of these events in the actual reality domain is observed and experienced, i.e. perceived events. These perceived events form the empirical reality domain. Positivism and social constructionism approaches operate only in the empirical reality domain. Critical realists believe that events or absence of them in the actual reality domain are actualised through interaction between generative or causal mechanisms (underlining relations, structures, mechanisms, tendencies). These generative mechanisms constitute the ‘real’ reality domain (Archer et al. 1998; Fletcher 2017; Mingers 2004).
The local uptake of DOACs is an example of a complex open system of processes involving various stakeholders and influenced by both internal and external factors. Understanding the reasons for the different rates of uptake of DOACs in differing health economies requires exploration of underlining causes and the relationship between what we experience and what actually occurs. The search for causation is the cornerstone of critical realism reflected in its ontological assumptions (Edwards et al. 2015; Fletcher 2017; Mingers 2004). Hence, critical realism informs the studies in this thesis to facilitates a better understanding of the studied phenomenon.

4.3.2 Epistemological assumption

Epistemological assumption refers to what counts as knowledge and how knowledge is known (Creswell 2013). In positivism, there is a single version of reality, which is independent and unaffected by the observer. The knowledge about reality is empirically acquired through observation or experiment. Therefore, knowledge claims about reality are limited to only what can be observed (Creswell 2013; Edwards et al. 2015; Mingers 2004). Whereas in social constructivism, the reality is subjective and entirely constructed socially through human interactions and individual experiences (Creswell 2013). Critical realists argue that both positivists and social constructivists prioritise epistemology over ontology (Edwards et al. 2015). In other words, reality is what we know (empirically observed or socially constructed). Whereas critical realists argue that human knowledge captures only part of reality and events exist with or without human knowledge, i.e. knowledge is different from being (Edwards et al. 2015; Fletcher 2017; Mingers 2004). Thus, the epistemological assumption in critical realism combines “epistemological relativism” and “judgemental rationalism” (Mingers 2004; Sorrell 2018). Epistemological relativism claims “human knowledge is socially produced, historically transient, and fallible” (Sorrell 2018, p.1268) and judgemental rationalism states “there are rational grounds for preferring some theories and explanations over others” (Sorrell 2018, p.1268).

According to critical realists, knowledge is context dependent as it is socially constructed, transient, and fallible (Fletcher 2017; Mingers 2004; Sorrell 2018). All social entities are thought to have causal powers that can lead to events in the actual reality domain. These causal powers are exercised only at particular times and contexts. Changes in the context will affect causal mechanisms leading to the presence or absence of events and thus different outcome. Therefore, critical realists
state that social systems are interactive and open (Fletcher 2017; Mingers 2004) and focus on understanding generative mechanisms to explain the studied phenomenon (Edwards et al. 2015; Fletcher 2017; Mingers 2004).

Critical realists reject “judgemental relativism” by claiming that all knowledge is not equally valid. Instead, they believe that some knowledge is a more accurate representation of reality than other knowledge. Rational grounds are used to choose between competing theories to explain more accurately the studied phenomenon (Edwards et al. 2015; Fletcher 2017; Mingers 2004; Sorrell 2018).

As critical realists subscribe to “judgemental rationalism”, critical realism research is not theory-determined. Instead, the theory is used for explanatory benefits to facilitate the discovery of knowledge for a better explanation of reality (Fletcher 2017; Mingers 2004) rather than to predict reality (Mingers 2004). Thus, the theory or theoretical framework used in critical realism research can be rejected or adapted to provide a better explanation of the studied phenomenon (Fletcher 2017).

4.3.3 Axiological assumption

Axiological assumptions are concerned with the role of values in research (Creswell 2013; Hiles 2012). All researchers are thought to bring values and beliefs that guide and affect the conduct of research (Creswell 2013). In particular, in critical realism, the researcher adopts “judgemental rationalism” and is empowered to decide which accounts of research participants are a better representation of reality. Such decisions will be influenced by the researcher’s political, personal, and intellectual perspectives (Parr 2015). Hence, acknowledgement of them through reflexivity is argued to increase the trustworthiness of or add rigour to the research study (Creswell 2013; Hiles 2012; Rae and Green 2016). Reflexivity is recommended throughout the research process, particularly considered before starting the project, during data collection and analysis (Rae and Green 2016). The following section outlines the motivation of the researcher to undertake the research, beliefs, and values related to the topic under investigation in this thesis. According to Rae and Green (2016), this will be classed as pre-research reflexivity.

The researcher (KM) in this study is a healthcare professional working predominantly in a hospital setting as a pharmacist. She is not regularly involved in the care of patients with AF requiring oral anticoagulants for stroke prevention. Her involvement
was limited to patients with AF admitted to non-cardiology wards she was working on. When needed, the researcher, in her professional capacity, would advise the medical team on the appropriate oral anticoagulation regime, e.g. dose adjustments in renal impairment, change of oral anticoagulant agent. The recommendations would follow local and national guidelines and would be in line with the local hospital trust medicine formulary. Therefore, she had limited awareness of the AF condition and the impact of oral anticoagulants on patient daily lives but knew the significance of preventing AF-related strokes.

The awareness of national recommendations for prescribing oral anticoagulants (warfarin and DOACs) highlighted discrepancies with the local hospital medicine formulary recommendations. The researcher observed a preference for a particular oral anticoagulant within her local Trust and a lack of patient choice of oral anticoagulants. The researcher believes that all patients should have equal access to nationally recommended medicines regardless of where they live. Also, an oral anticoagulant that suits them the best, e.g. compatible with their lifestyle, should be offered. These observations provoked interest and motivation in exploring reasons for the varied uptake of DOACs between different health economies despite the same national recommendations.

The researcher's initial thoughts on the variability regarding oral anticoagulants availability were due to the much higher acquisition cost of DOACs compared to warfarin. After consulting available literature on the topic, she realised that the process of implementing a new medicine into practice was complex with a wide range of actors involved. Hence, it was anticipated for the reasons for the variable uptake of DOAC to be multifactorial. Therefore, a qualitative methodology with semi-structured interviews was selected, despite the researcher being more familiar and confident with quantitative research inquiry.

4.3.4 Methodological assumption

The methodological assumption is concerned with the process of research (Creswell 2013). This study has employed a qualitative research approach underpinned by a critical realism theoretical perspective. The Diffusion of Innovations in Service Organisations model by Greenhalgh et al. (2004) was used as a conceptual model in the study.
4.3.4.1 Rationale for qualitative research approach

A qualitative rather than quantitative research approach was selected for this study to explore and understand barriers and enablers to the uptake of DOACs within the studied health economies. Qualitative research inquiry focuses on exploring perspectives of participants ascribed to the phenomenon being studied (Creswell 2013). In contrast, quantitative research is concerned with testing theories and predetermined hypothesis by employing a deductive approach and positivism philosophical framework (Creswell 2013).

The systematic review findings presented in Chapter 2 identified several factors affecting the uptake of new medicines into health economies. The reviewed studies were mainly quantitative and used secondary data from routinely collected prescribing or insurance claims databases. Thus, the identified factors affecting the uptake of new medicines were limited to the descriptive information contained within the secondary data or closed-ended questions in surveys. Thus, these studies failed to explore factors affecting the uptake of new medicines that were not captured by regularly collected secondary data, e.g. factors that cannot be observed but are experienced or casual mechanisms affecting the use of new medicines.

Furthermore, patients are an essential part of the healthcare system. Still, evidence on their role in the uptake of DOACs is scarce, as demonstrated in the literature review findings in Chapter 3. Hence, qualitative research is more appropriate as there is little known about the extent to which patients influence the uptake of new medicines.

Although a critical realist philosophical framework is not attributed to a specific methodology (Sorrell 2018), the researcher believes that qualitative rather than quantitative research methods would be more appropriate for uncovering generative mechanisms for identified factors affecting the uptake of DOACs. The data collected through qualitative research methods, i.e. semi-structured interviews, would supplement and expand the current understanding of the factors affecting the uptake of new medicines such as DOACs.

4.3.4.2 Conceptual framework

Following the critical realism philosophy, a conceptual framework was used as an initial theory to guide the research study (Fletcher 2017). Thus, during the process of the research, the theory was adapted and modified to achieve a better representation
of the studied phenomenon. The conceptual framework selected to guide the research was the Diffusion of Innovations in Service Organisations model by Greenhalgh et al. (2004). The authors of the model also recommend using it as "illuminating the problem and raising areas to consider" rather than "providing the definitive answers". (Greenhalgh et al. 2004, p. 613-614).

This model was selected because it was developed from a comprehensive systematic review of published empirical studies from 13 different research areas that explored the diffusion of health service innovations (Greenhalgh et al. 2004). Furthermore, the model built on and extended the Diffusion of Innovations theory by Rogers (1962) and has been extensively used in healthcare research.

The Diffusion of Innovations theory by Rogers (1962) explains the diffusion of innovations within a social system. Diffusion was defined as "the process by which an innovation is communicated through certain channels over time among the members of a social system" (Rogers 1962, p.10). The theory states that four main elements are influencing the process:

- Innovation: a new practice, idea, or object with perceived attributes of relative advantage, compatibility, complexity, trialability, and observability, as well as its potential for reinvention.
- Communication channels: the ways the information about the innovation is communicated to potential adopters, e.g. mass media, interpersonal channels.
- Time: concerned with time from learning about the innovation to its adoption or rejection. Four adopter categories were identified: innovators, early adopters, early majority, late majority, and laggards.
- Social system: "a set of interrelated units that are engaged in joint problem solving to accomplish a common goal" (Rogers 1962, p.24). Aspects of social system influencing the diffusion are the social structure, system norms, opinion leaders, and change agents.

Greenhalgh's et al. (2004) model focused on the diffusion of innovations in a healthcare setting aiming to "improve health outcomes, administrative efficiency, cost-effectiveness, or users' experience and that are implemented by planned and coordinated actions" (p.582). The model proposes nine interacting elements influencing the diffusion of innovations: the innovation, adoption by individuals,
assimilation by the system, communication and influence, system antecedents for innovation, system readiness for innovation, the outer context (inter-organisational networks and collaboration), implementation process, and linkage among components of the model. The model with its elements is visually presented in Figure 4.4.
Figure 4.4 Diffusion of Innovations in Service Organisations model in health service and organisation by Greenhalgh et al. (2004). Reproduced with kind permission from Greenhalgh et al. (2004), copyright held by Milbank Memorial Fund.
4.4 Patient and Public Involvement

Patient and Public Involvement (PPI) is an active involvement of service users in research where they contribute to the development, coordination, and delivery of research (Haeys et al. 2012). The recognition of PPI in improving the quality of research studies is growing, and it is expected to be a standard in health and social research in the UK (Haeys et al. 2012), including doctoral research (Tomlinson et al. 2019).

PPI has been shown to enhance the quality and relevance of research by service users bringing their “lived experiences” and perspectives that may differ from researchers (Baxter et al. 2016; Brett et al. 2012; Ocloo and Matthews 2016). Consequently, PPI is thought to decrease unsuccessful and wasteful research by providing their perspectives on priorities for research (Crowe et al. 2015; Tallon et al. 2000). The positive impact of PPI has been shown in all stages of research, including identifying research priorities, design and delivery of the project, and implementation and dissemination of research findings (Brett et al. 2012). Therefore, PPI was utilised at the design stage of this research project, and PPI advisory group was formed to inform the development and delivery of the project.

4.4.1 PPI at the research design stage

The aim of PPI at the research design stage was:

- To confirm whether the identified research topic was relevant to service users.
- To identify relevant and meaningful potential outcomes of the research project.
- To discuss recruitment strategies.
- To highlight potential ethical issues.

Consultation with service users with non-valvular AF and taking an oral anticoagulant was held in health economies A and B. In health economy C, a consultation with service users was organised. Still, no participants expressed interest in taking part.

In health economy A, a local patient support group for people with AF was identified through an internet search of hospital patient support groups, charity groups, and general patient groups. The lead of the programme was contacted via email, who then obtained consent from members of the group for the researcher to attend one of their regular meetings to discuss the research proposal.
Six members of the group attended the two-hour meeting with AF (three male and three female). Two patients were taking warfarin, three patients were taking a DOAC, and one patient had been recently diagnosed with AF and was not taking any oral anticoagulant. The group members were asked open questions allowing them to comment and share their experiences on commencing and taking oral anticoagulants. Specific aspects of the study, e.g. methods, recruitment strategy, proposed study plan, were also discussed.

In health economy B, a patient support group such as in health economy A was not found. Therefore, one-to-one discussions of up to 15 minutes with patients, attending outpatient arrhythmia clinic, were held. Local Trust's approval was acquired, and an arrhythmia nurse first approached patients. Five patients were approached, and four (all male) agreed to speak with the researcher. One patient was taking warfarin, one a DOAC, and two patients were started on a DOAC during the clinic appointment.

Consultation with service users confirmed the relevance and importance of the proposed research study. Their shared "lived experiences" indicated there might be an unexplained variability of oral anticoagulant choices in the studied health economies. Also, their experiences of being involved in decision-making about oral anticoagulants were in line with the narrative literature review findings (Chapter 3). Moreover, they highlighted that additional healthcare professional groups (e.g. nurses, pharmacists) should be included in the data collection stage as these individuals played an important role in patients with AF care. As a result, the recruitment strategy for healthcare professionals was amended to include nurses and pharmacists, in addition to doctors. The participants identified no ethical or safety issues, and the proposed recruitment strategy was deemed to be acceptable to them. At this stage-specific study, outcomes were not identified, but it increased the researcher's understanding of service users' experiences. This insight was used as a springboard to further project development and the formation of a PPI advisory group.

4.4.2 PPI advisory group

A PPI Advisory group was formed of three members (two females and one male) diagnosed with AF and taking an oral anticoagulant (warfarin or a DOAC). Two members were recruited from the initial consultation at the research design stage and the third member from a lay member panel of another large research programme.
Each member of the PPI Advisory group was provided with a developed Terms of the Reference document outlining objectives, expected commitment, and reimbursement, which was in line with INVOLVE guidance (Hayes et al. 2012).

The PPI Advisory group aimed to support the project throughout its conduct and act as a "critical friend". The group and the researcher met twice a year (in total six meetings) and were involved in project development, delivery of the project, and dissemination of research findings.

During the project development stage, the PPI members and the researcher co-designed a participant information sheet and a consent form for patients in plain English. They also discussed recruitment strategies, reviewed a proposed interview schedule for patients, and validated narrative literature review findings. During the delivery of the project, the PPI advisory group members were actively involved in the recruitment of patients through local patient support groups and analysis of interviews with patients. The group's involvement during the dissemination of research findings included co-developing lay summaries of main research findings and presentation of the results to local patient support groups.

4.5 Data collection

Data sources included non-participant observations, routine documents (e.g. meeting minutes, local clinical guidelines), and semi-structured interviews.

4.5.1 Meeting observations and collection of relevant documents

Observational research as a data collection method involves observation of participants in their natural setting with note-taking on what has been observed (Austin and Sutton 2019). Observations can be used in quantitative (e.g. structured observations) and qualitative (e.g. ethnography) research (Mligo 2016). During observations, the researcher can take an active role by becoming part of the studied group or a non-participatory role by remaining outside the studied group (Austin and Sutton 2019; Mligo 2016).

Although the researcher had a limited prior understanding of the process of new medicine approvals within local NHS organisations, KM needed more information to develop recruitment strategies for potential participants. Therefore, the purpose of the observations of meetings, where medicines were discussed and approved for local use within the studied health economies, was to identify and recruit key stakeholders
involved in the process. The researcher attended the meetings without participation in the meeting, i.e. non-participant observations (Mligo 2016). Notes during observations were taken using a developed semi-structured observation guide (Appendix D). The observation guide development was informed by the systematic review findings (Chapter 2) and reviewed by the supervision team. The observation guide acted as a reminder to focus the note-taking on discussions around the implementation of NICE-recommended new medicines. These notes were used to supplement interview data with healthcare professionals and key stakeholders (Mligo 2016). Also, the meeting agenda and minutes when the use of DOACs was discussed were obtained. Observed meetings were not recorded.

Documents (clinical guidelines, policy documents) related to the implementation and use of DOACs within the studied health economies were also collected. These documents were used to supplement the interview data and identify healthcare professionals and key stakeholders to recruit for interviews. Trust formularies and websites were reviewed to identify relevant clinical guidelines. Also, relevant documents were identified during interviews with healthcare professionals and key stakeholders. Furthermore, observations, collected documents, and interviews with healthcare professionals and key stakeholders were used to map the approval process of new medicines within the studied health economies. The developed process maps were shared with medicine information pharmacists at local hospital Trusts to improve their accuracy. These maps were used to improve the understanding of the researcher on the local process for approving new medicines and highlight differences between the studied health economies. Thus, they informed semi-structured interviews and data analysis. An example of the developed process map is presented in Appendix E.

4.5.1.1 Number of meeting observations

Two main meetings, where medicines are approved for local use within the studied health economies, were attended during the scoping work. These meetings were Drug & Therapeutic Committee (DTC) meetings in secondary care and Area Prescribing Committee (APC) meetings in primary care. The DTC and APC meetings occur monthly in each health economy. The scoping work indicated that each meeting follows a standardised agenda format. Meetings are attended by the group members and occasionally by non-member healthcare professionals to present a case to be discussed. Due to the structured nature of meetings and monthly frequency, it was
anticipated that two observations of each meeting in each studied health economy would be sufficient to gain the needed knowledge.

4.5.1.2 Recruitment process

Chairs of DTC and APC meetings in each health economy were contacted via email and introduced to the researcher by a local collaborator. They were provided with an invitation letter, a participant information sheet (Appendix F), and a consent form (Appendix G). The chair of the meetings discussed the study with members of the committees. The committee members and chairs had 14 days to consider taking part in the study. If no response was received after 14 days, a reminder was sent. In total, two reminders would be sent before assuming that the invited committees did not wish to be observed. If the committee agreed to take part, the chair would contact the researcher via email or phone. The chair completed the consent form on behalf of the committee group.

4.5.2 Semi-structured interviews

Semi-structured interviews with patients, healthcare professionals, and other key stakeholders were used to identify factors affecting the uptake of DOACs within three different health economies in Yorkshire. Recruitment of and interviews with patients were conducted first, followed by recruitment of and interviews with healthcare professionals and key stakeholders.

Interviewing is widely used for data collection in qualitative studies (Gill et al. 2008; Kallio et al. 2016; Qu and Dumay 2011), especially in healthcare research studies (Gill et al. 2008). Qualitative interviewing allows a rich and in-depth exploration and understanding of the studied social phenomenon by accessing the views of participants (Edwards et al. 2015; Qu and Dumay 2011). The interaction between the researcher and the participant during the interview leads to "the mutual construction of meanings and possibility of the joint construction of knowledge about experiences, events, and activities" (Edwards et al. 2015, p.110).

One-to-one, rather than group interviewing, was employed in this study. Group interviewing or focus group is another commonly used method of interviewing in qualitative research. This approach explores collective views on the studied research topic and involves group discussion guided by the researcher (Gill et al. 2008). Focus groups are less suitable for studying sensitive topics as participants may not want to
disclose their perspectives in a group environment (Gill et al. 2008) or will be influenced by other participants leading to socially desirable responses (Avocella 2012). The studied research topic in this study was deemed to be a sensitive topic for participants as it explored the personal experiences of patients and prescribing practices of healthcare professionals. Therefore, a focus group was discounted as a data collection method for this study.

Observational or ethnographic research techniques were discounted too. Data collection through in-depth observations of participants in a naturally occurring environment was not possible due to retrospective experiences of participants being explored. Whereas one-to-one interviewing allowed for participants to share their retrospective experiences.

There are three main types of qualitative one-to-one interviews: structured, unstructured, and semi-structured (Qu and Dumay 2011). Structured interviews follow an interview schedule with a set of predetermined and explicit questions. All interviewed participants are asked the same questions in the same order, and the researcher is not permitted to deviate from the interview schedule. Structured interviews are rigid and yielding brief responses that limit the capture of in-depth and rich data. Thus, they are seen as verbal questionnaires and argued to be more suitable in quantitative rather than qualitative research (Gill et al. 2008; Qu and Dumay 2011; Ryan et al. 2009).

In contrast, unstructured interviews, also known as informal, do not follow a set of questions. Instead, the conversation is led by a participant, and the researcher asks open-ended questions based on the participant's given answers. Unstructured interviews are time-consuming and best employed when little to none is known about the studied phenomenon, and questions cannot be prepared in advance (Gill et al. 2008; Ryan et al. 2009). Between structured and unstructured interviews sit semi-structured interviews. Semi-structured interviews are the most commonly used type of interview in qualitative research (Gill et al. 2008; Qu and Dumay 2011). An interview guide with predetermined key questions or topics to cover is employed. The interview guide helps to focus the conversation on covering the identified broad research themes of interest to the researcher (Gill et al. 2008). Semi-structured interviews are also more flexible than structured interviews with follow-up questions and probes adapting to what the participant is saying to evoke more in-depth responses and
explore unexpected issues raised by participants (Gill et al. 2008; Kallio et al. 2016; Qu and Dumay 2011; Ryan et al. 2009). As the researcher aimed to collect in depth and rich data and identified themes to explore with participants from conducted literature reviews, semi-structured interviews were deemed to be the most appropriate method of interviewing.

As a result of the interview guide being flexible and adaptable, the interview guide used in this study evolved through the data collection process. It was informed by new insights gained in earlier interviews but not captured by the initial interview guide. Thus, the interview process not only documented the perspectives of participants on the studied topic but also compared, contrasted, or expanded on the insights gathered from other participants to gain a more comprehensive understanding of barriers and enablers affecting the uptake of DOACs. Such an approach to qualitative interviewing is thought to align with critical realism philosophy (Edwards et al. 2014). Overall, the semi-structured interviews allowed a consistent and systematic approach to data collection across interviews and at the same time emergence of new information from unique experiences of participants (Gill et al. 2008; Qu and Dumay 2011).

The topic guides for semi-structured interviews were developed for each participant group. The development included five interlinked phases as described by Kallio et al. (2016) to increase the trustworthiness or rigour of the study. Firstly, a semi-structured interview was deemed an appropriate data collection method in this study as perceptions of participants on the factors affecting the uptake of DOACs would be explored. The second phase involved retrieving previous knowledge on the studied topic to gain a good understanding of possible factors affecting the uptake of DOACs. It was achieved by conducting narrative and systematic literature reviews (see Chapter 2 and Chapter 3). The third phase consisted of developing an initial draft of the interview guide, which was pilot tested in the fourth phase to ensure relevance and improve the wording of questions.

The interview guide for patient participants was critiqued by the PPI advisory group and resulted in improved lay language and inclusion of visual prompts for two questions. The final interview guide consisted of eight open-ended questions with prompts and probes (Appendix H). Two questions had visual prompts: 1) pictures of different oral anticoagulant medicine packages and 2) visual presentation of three different styles of consultations (doctor-led, shared-decision, patient-led). The open-
ended questions explored the patient's experience of consultation when an oral anticoagulant was started, their knowledge of available oral anticoagulants, and views on the availability of new medicines, including DOACs.

The supervision team reviewed the interview guides for healthcare professionals and key stakeholders. The interview guide for healthcare professionals consisted of ten open-ended questions with several prompts and probes (Appendix I). The open-ended questions explored healthcare professional's practice concerning the use of oral anticoagulants, availability of DOACs, and their views on barriers and facilitators to the use of DOACs. The interview guide for key stakeholders consisted of six open-ended questions with several prompts and probes (Appendix J). The open-ended questions explored the process of implementing DOACs and factors affecting the uptake of DOACs within the studied health economy.

4.5.2.1 Sampling strategy

Probability sampling techniques often used in quantitative research are argued to be incompatible with qualitative inquiry (Luborsky and Rubinstein 1995; Patton 2015). Therefore, non-probability sampling techniques are employed. There are various non-probability sampling strategies used in qualitative research (Creswell 2013; Luborsky and Rubinstein 1995; Patton 2015). The most common types identified in the literature are convenience, snowballing, quota, case study, and purposive sampling (Luborsky and Rubinstein 1995). However, Patton (2015) argues that all sampling strategies in qualitative inquiry are purposive as information-rich cases are purposefully selected to answer the research questions.

Purposive sampling, more specifically, theoretical sampling, was employed in this research study. Theoretical sampling originated from grounded theory methodology. The sample is purposefully selected to inform emerging theory during simultaneous collection and analysis of data (Coyne 1997). Hence, it was appropriate for the study in this thesis, as there was little known about the studied phenomenon. The first theoretical sampling step was to identify initial participants experiencing the studied phenomenon by using predetermined inclusion and exclusion criteria.

Identified categories informed further sampling decisions during simultaneous data analysis and collection. Participants were selected to develop identified categories in the emerging theory until theoretical saturation was reached (Coyne 1997).
Theoretical saturation is reached when collected data adds no new information to the developed categories in the emerging theory (Charmaz 2014; Creswell 2013).

4.5.2.2 Sample size

The sample size in qualitative research varies between different methodologies and sampling strategies employed (Creswell 2013; Sandelowski 1995). Although the sample size in theoretical sampling is determined by theoretical saturation, there are suggestions of a minimum sample size to inform designing research protocols.

Creswell (2013) recommends studying at least 20 to 30 cases to "develop a well-saturated theory" (p.157), whereas Bertaux (1981) cited in Guest et al. (2006:61) states that the minimum sample size in qualitative research should be 15. Guest et al. (2006) study showed that data saturation could be reached with 12 interviews when a relatively homogenous population is studied, and research objectives are narrow. However, larger sample sizes may be needed for studies with broader objectives, low sample specificity, or conducted by less experienced researchers (Guest et al. 2016; Malterud et al. 2016).

Guest et al. (2016) used the term data saturation rather than theoretical saturation. The latter refers to theory generation in grounded theory methodology whereas data saturation is a more general term indicating "the point in data collection and analysis when new information produces little or no change to the codebook" (Guest et al. 2016, p.65). Thus, the final sample size in the study described in this thesis was determined by data saturation.

Although the final sample size was determined by data saturation, the preliminary sample size was required for research planning. It was informed by recommendations discussed earlier and previous research with similar objectives. Studies reporting on patient involvement in decision-making about oral anticoagulants for stroke prevention in AF required 11 to 21 participants to reach data saturation (Clarkesmith et al. 2017; Dantas et al. 2004; Xuereb et al. 2016). Previous studies on new medicine prescribing or implementation of guidelines interviewed between 20 to 30 healthcare professionals (Broom et al. 2016; Prosser and Walley 2003). Therefore, a preliminary sample size between 20 to 25 for each participant group (patients, healthcare professionals, key stakeholders) was expected to achieve data saturation.
4.5.3 Interviews with patients

The first group of participants included patients with non-valvular AF taking an oral anticoagulant, warfarin, or a DOAC. Patients are end-users of prescribed medicines and can play a role in the uptake of DOACs through their involvement in the decision-making about the choice of oral anticoagulation therapy. Hence, patients' perspectives on factors affecting the uptake of DOACs are important to explore as they may reveal factors not visible from the accounts of healthcare professionals or key stakeholders.

4.5.3.1 Inclusion and exclusion criteria

The following inclusion criteria were used to recruit patients for the study:

- Adult patients (>18 years) diagnosed with non-valvular AF;
- Prescribed an oral anticoagulant (vitamin K antagonist (e.g. warfarin) or a DOAC);
- Living in one of the studied health economy areas;
- Able to give informed consent;
- Understand written and spoken English or have a family member willing to interpret.

Patients that were deemed to be inappropriate to include in the study by their direct care team (e.g. end-of-life care patients, patients with dementia) were excluded.

4.5.3.2 Recruitment process

Up to 30 patients were approached in each health economy by a member of their direct care team, a nurse, or a pharmacist. The initial aim was to recruit eight patients from each health economy. Three recruitment approaches were identified and employed. The recruitment approach was matched to the local practice of initiating oral anticoagulants for stroke prevention in non-valvular AF in each health economy. Participants were offered reimbursement for their travel expenses if required, and a £10 high-street voucher as a token of appreciation for taking part. The PPI Advisory group had recommended it.

Recruitment from outpatient clinics at local hospital Trusts

Patients recruited in hospital Trusts were approached in outpatient clinics (anticoagulation or arrhythmia). A healthcare professional (nurse or pharmacist) working in the clinic identified and approached eligible patients using the inclusion and
exclusion criteria. The healthcare professional introduced the study to the patient and provided a participant information sheet (Appendix K) with a consent form (Appendix L) and a pre-paid return envelope. Interested patients could contact the researcher by phone, email, or post. The researcher contacted patients who expressed an interest by phone to explain the study in detail and answer any questions they might have. If the patient agreed to take part and complete and return a consent form, a date for the interview was arranged by phone. This recruitment approach was used in health economies B and C.

Recruitment from GP practices

Patients in general practice were recruited from GPs’ anticoagulation clinics. A healthcare professional (nurse or pharmacist) working in the clinic identified and approached eligible patients using the inclusion and exclusion criteria. The healthcare professional introduced the study to the patient and provided a participant information sheet with a consent form and a pre-paid envelope. Interested patients contacted the researcher by phone, email, or post. The researcher contacted patients who expressed interest by phone to explain the study in detail and answer any questions they might have. If the patient agreed to take part and complete and return a consent form, a date for the interview was arranged by phone. This recruitment approach was used in health economy A. The researcher contacted managers of four general practices via email and sent a letter of invitation with a participant information sheet. One GP practice with a warfarin clinic agreed to take part. The statement of activities agreed with the recruited GP practice was treated as written consent for their team member to identify and recruit patients for the study. The GP practice was paid £150 for the time that their team member spent on identifying and approaching eligible patients in the anticoagulation clinic. A total of 30 patients were approached in the clinic.

Recruitment from a patient support group

The PPI advisory group members attended a local patient support group for patients with arrhythmias in health economy A. They identified and approached eligible participants within the patient support group and provided them with participant information sheets, consent forms, and pre-paid return envelopes. Interested patients contacted the researcher by phone, email, or post. The researcher contacted patients
who expressed an interest by phone to explain the study in detail and answer any questions they might have. If the patient agreed to take part and complete and return a consent form, a date for the interview was arranged by phone. This recruitment approach was used in the health economy A.

4.5.4 Interviews with healthcare professionals

The second group of participants consisted of healthcare professionals involved in the care of patients with non-valvular AF requiring oral anticoagulants for stroke prevention. These healthcare professionals were prescribing, recommending, or advising oral anticoagulants to patients. Interviews with healthcare professionals were anticipated to reveal how they make decisions to prescribe or recommend a specific oral anticoagulant and what influences their decision and thus the uptake of DOACs.

4.5.4.1 Inclusion and exclusion criteria

The following inclusion criteria were used to recruit healthcare professionals:

- Profession - any of the following: hospital doctor, general practitioner, nurse, or pharmacist (hospital, GP, community setting);
- Involved in care of patients with non-valvular AF requiring oral anticoagulants for stroke prevention (e.g. prescribing medicines, advising on medical treatment, monitoring);
- Practices in one of the studied health economy areas.

Healthcare professionals practising outside the NHS, e.g. private practice, were excluded.

4.5.4.2 Recruitment process

The initial aim was to recruit eight health care professionals from each health economy. Two recruitment approaches were identified and employed in all three health economies. Participants were offered reimbursement for their travel expenses if required. No payment or reimbursement for their time was offered.

Recruitment via NHS staff members

The researcher and the supervision team identified eligible healthcare professionals for the study through their clinical networks of the research team, relevant documents review, observations of meetings, and conducting interviews. Clinically practising members of the supervision team and independent NHS staff members approached
eligible participants within their clinical practice via email on behalf of the researcher. Interested participants were contacted by the researcher via email and provided with a participant information sheet (Appendix M) and consent form (Appendix N). If the interested participant agreed to take part and complete a consent form, a date for the interview was arranged via email or phone.

Recruitment via social media
Brief information about the study (Appendix O) was published on social media platforms, Twitter and Facebook, from the researcher’s personal account. Interested participants would contact the researcher for more information, and the researcher would check their eligibility, explain the study in detail, and provide a participant information sheet with a consent form and pre-paid return envelope if needed. If the participant agreed to take part and complete a consent form, a date for the interview would be arranged via email or phone.

4.5.5 Interviews with key stakeholders
The third and last group of participants included other key stakeholders that played roles in decisions about the use of DOACs at a local organisation in the studied health economies. Interviews with this group of participants were anticipated to provide insights into organisation level factors influencing the uptake of DOACs.

4.5.5.1 Inclusion and exclusion criteria
Key stakeholders included NHS staff involved in the implementation of DOACs (e.g. DTC and APC members), producing or disseminating documents (e.g. guidelines) related to the implementation of DOACs within all three health economies. This group of participants also included representatives of pharmaceutical industry companies who manufactured DOACs and the patient support group leads with an interest in supporting patients with AF in the studied health economies.

4.5.5.2 Recruitment process
The initial aim was to recruit eight key stakeholders from each health economy. Participants were offered reimbursement for their travel expenses if required. No payment or reimbursement for their time was offered. The same recruitment approach was employed in all three health economies. The researcher and the supervision team identified potential key stakeholders for the study through their clinical networks, relevant document reviews, observations of DTC and APC meetings, and the HCP
interviews. Members of the supervision team (KS and DP) and independent NHS staff members approached eligible participants within their clinical practice via email on behalf of the researcher. Interested participants were contacted by the researcher via email and provided with a participant information sheet (Appendix P and Appendix Q) and a consent form (Appendix N).

Potential participants working outside the NHS, e.g. representatives of pharmaceutical companies, were sent invitation emails with a participant information sheet and a consent form by the researcher. If no response was received within two weeks, a reminder email was sent by the researcher. If no response is received to the first reminder after two weeks, a second reminder was sent. If no response was received to the second reminder, it was assumed that the potential participant did not want to take part. If the interested participant agreed to take part and complete a consent form, a date for the interview was arranged via email or phone.

4.6 Data analysis

Thematic analysis is commonly used in qualitative data analysis (Nowell et al. 2017). It is not bound to any specific theoretical grounding and is accessible to researchers new to qualitative research. Also, it is particularly useful when perspectives of different participants are analysed as in the study described in this thesis (Braun and Clark 2006; Nowell et al. 2017). The thematic analysis approach is criticised for its flexibility and opacity, which can potentially result in a lack of rigour during the data analysis process (Nowell et al. 2017; Ward et al. 2013). To bring rigour and transparency to the data analysis process, a framework analysis method, which is a structured form of thematic analysis, was employed in this research (Ritchie et al. 2014).

4.6.1 Framework method

The Framework method is systematic and provides a clear structure for data management. It facilitates the development of themes that can be easily linked back to the original data, thus minimising potential researcher bias (Gale et al. 2013; Parkinson et al. 2016; Ritchie et al. 2014). It also provides a clear audit trail to the analysis process, hence contributing to the rigour or trustworthiness of the data analysis (Nowell et al. 2017; Ritchie et al. 2014).

The method, unlike others, e.g. grounded theory, phenomenology, is not bound to any particular theoretical frameworks or philosophical ideas. Thus, it can be used in any
qualitative data analysis which aims to generate themes (Gale et al. 2013; Ritchie et al. 2014; Ward et al. 2013). It has also been widely used in health care research with textual data, mostly with semi-structured interview data (Gale et al. 2013; Ritchie et al. 2014; Ward et al. 2013). The study described in this thesis uses textual data from semi-structured interviews and extracts from documents. It aims to generate themes to understand and explain factors affecting the uptake of DOACs.

However, the method has been criticised for being a time-consuming and resource-intensive approach (Gale et al. 2013; Parkinson et al. 2016; Ward et al. 2013). Additionally, the analytical process could become a process rather than outcome-focused (Parkinson et al. 2016). To prevent this, the researcher kept focused on the research question during the analysis (Parkinson et al. 2016), involved the supervision team in analysis discussions, and kept a reflective journal to record emerging ideas during the data collection and analysis. The use of a reflective journal is argued to increase rigour in the study by providing an additional audit trail for decisions on how themes were developed (Ward et al. 2013). Also, reflexive journaling promoted being reflective and critical throughout the data analysis process, which in turn to recognising and addressing the effect of the researcher's belief and values on the data analysis (Nowell et al. 2017).

Gale et al. (2013) argue that researchers need to be well trained to apply this method successfully but others argue that it is a good tool for researchers new to qualitative research (Parkinson et al. 2016; Ward et al. 2013). Nevertheless, the researcher of this study attended an in depth two-day course on the application of the Framework method. Furthermore, supervisors with experience in using it were involved in the analysis process and advised the researcher.

The Framework method consists of five inter-related stages that can be broadly divided into data management and data interpretation phases (Ritchie et al. 2014; Ward et al. 2013) (Figure 4.5). Each stage of the process is described in detail in later sections. The completion of data management and interpretation was facilitated by a computer-assisted qualitative data analysis software, NVivo (version 11).
4.6.1.1 Data management

The first three stages of the Framework Analysis method are classed as data management (Figure 4.5). The data management phase aims to make the data accessible for interpretation by re-ordering, condensing, and prioritising relevant information to the research question. At the same time, retaining links to the original data (Ritchie et al. 2014).

The first stage is (re-) familiarisation with the dataset through immersion in the data to get a sense of what is going on (Gale et al. 2013; Ritchie et al. 2014; Ward et al. 2013). The researcher conducted all the interviews and transcribed verbatim some of the interviews. The majority of the interviews were transcribed verbatim by a professional
transcription agency. The researcher checked all transcribed verbatim interviews by listening to audio recordings and rereading the transcripts to ensure their accuracy and to re-familiarise herself with the dataset. This way, the researcher ensured that interviews from all participants were considered in the analysis.

The second stage was the development of an analytical framework. The analytical framework was used to manage and organise the data to summarise and reduce it in a meaningful and manageable way (Gale et al. 2013; Ritchie et al. 2014). The creation of the framework involved inductive and deductive approaches. Initially, data from interviews with patients and data from interviews with healthcare professionals and key stakeholders were analysed separately. Thus, two analytical frameworks were developed.

Firstly, several transcripts sampled for diversity and richness were read and coded line-by-line (open coding) by the researcher and one member of the supervision team (SR). Those codes were used to develop preliminary categories and sub-categories that best fitted the data related to the research questions (inductive process). Then, preliminary categories and sub-categories were compared to the interview schedules, literature review findings (see Chapter 2 and Chapter 3), and the conceptual framework to refine the developed analytical frameworks (deductive process). Additionally, the PPI Advisory group members coded three patient interviews, and their coding was also used to refine the analytical framework for the patient interview dataset (Tomlinson et al. 2019). The refined analytical frameworks were piloted with five interviews and further refined until no additional categories emerged. The “Other” category was added to organise data that did not fit in the established categories. The finalised analytical frameworks (Appendix R and S) were applied to all transcripts and extracts from documents.

The third stage of data management is indexing, which involves applying the analytical framework categories to the full dataset. The researcher read all transcripts in depth and organised the data into categories of the developed analytical frameworks.

The fourth and last stage of data management was charting. During charting, the researcher systematically summarised and hence reduced the data from each transcript. The summaries were displayed on a matrix by both category and case (individual interviewee) with links to the original data. The matrix was reread
afterwards to ensure clarity, the balance of information, and emphasis. The finalised matrix was used for data interpretation.

4.6.1.2 Data interpretation

The last stage of the Framework Analysis method was data interpretation; the move from data management towards understanding and explaining the data (Ritchie et al. 2014). Before starting data interpretation, the researcher reviewed field notes, her reflective journal, revisited the research objectives, and developed an analytical plan. Then, the researcher started the descriptive analysis by identifying similarities and differences between and across cases and developed typologies where appropriate. Through the process, the researcher tested it and noted when data saturation was reached (Guest et al. 2006, p.65).

After the descriptive analysis, the researcher moved towards explanatory analysis by looking for emerging patterns and connections across cases. In line with the critical realism ontology, the researcher focused on casual mechanisms or conditions to develop explanations for the identified barriers and enablers to the uptake of DOACs within the studied health economies.

During the process, potential themes and sub-themes were generated from the data through coding (inductive process). Literature review findings (Chapter 2 and Chapter 3) and the conceptual framework were employed to explain further and refine the developed themes (deductive process). The credibility and clarity of the interpretation were checked by discussing the interim and final analysis results with the supervision team (BF, DP, KS, MR, SR), the PPI advisory group, and Medicine Optimisation Research Group members.

4.7 Identifying potential toolkit components of a toolkit

The findings of literature reviews and empirical studies of this thesis were mapped to the Diffusion of Innovations in Service Organisations model by Greenhalgh et al. (2004) (described in section 4.3.4.2) to identify potential components of a future toolkit. The toolkit would aim to facilitate the uptake of cost-effective new medicines into clinical practice by setting out practical recommendations to clinicians and local organisation decision-makers to support the uptake of new medicines.

Although the Diffusion of Innovations in Service Organisations model provided descriptions for most of its elements, some lacked operational definitions. Cook et al.
(2012) provided working definitions for all elements of the model. These working definitions were used to operationalise the model during the mapping process (see Chapter 7).

Firstly, the findings of the interviews reported in Chapter 5 and 6 were reread in detail to identify factors that were perceived to influence the uptake of DOACs. If clarification was needed, the researcher referred back to the summaries produced during the data analysis. Anything that study participants identified as supporting or hindering the use of DOACs was labelled as a factor. The identified factors were presented as barriers, facilitators, or had no attribute as they could be either a barrier or a facilitator. Secondly, the descriptions of the model were used to identify to which elements of the model the identified factors fitted the best. Thirdly, the factors reported in the literature, findings presented in Chapter 2 and 3, were also mapped to the elements of the model. They were not presented as either a barrier nor facilitator due to many of them having a varied impact across different reviewed studies. Fourthly, the identified factors from empirical and literature review findings attributed to each element of the model were considered together to propose a potential component for inclusion in the future toolkit.

Elements with no factors mapped from this study findings were excluded from consideration for inclusion in the toolkit development. Also, elements of the model deemed not to be relevant by the researcher to the future toolkit were discussed with members of the supervision team (BF, KS, SR) to achieve a decision if to exclude or include them.

The identified factors in this thesis that did not fit the elements of the model were grouped into themes. Then, identified factors from empirical and literature reviews were mapped to these themes and potential components for the toolkit were identified.

The initially identified potential components during the mapping process were reviewed and further refined to prevent components from overlapping with each other. Once a final set of potential components was developed, action points based on empirical findings for each component were suggested.

4.8 Researcher biases and quality assurance

There is a continuous debate and a lack of consensus about the best way to assess quality in qualitative research (Nowell et al. 2017; Mays and Pope 2000; Reynolds et al. 2011; Tracy 2010). Most quality assurance approaches focus on assessing the
quality of research outputs rather than the research process (Reynolds et al. 2011). The quality of research outputs is demonstrated by meeting certain criteria thought to indicate research quality (Reynolds et al. 2011). Lincoln and Guba (1985) developed criteria of credibility, dependability, transferability, and confirmability to demonstrate the trustworthiness of a qualitative study and this is frequently used by qualitative researchers (Nowell et al. 2017; Reynolds et al. 2011). These criteria are seen as alternatives to validity, reliability, generalisability, and objectivity terms used in quantitative research (Hadi and Closs 2016; Nowell et al. 2017; Reynolds et al. 2011).

Credibility refers to accuracy and the plausibility of the results reflecting the perspectives of participants (Tracy 2010). As presented earlier, the lead researcher (KM) was a practising pharmacist during the project and her preconceptions (discussed in 4.3.3 section) may have influenced the data collection and analysis. Interviewed participants were aware that KM was a pharmacist (not involved in the care of the interviewed patients or working with the interviewed participants) and thus they might not have shared their views on the researched topic in full. For instance, patients might have not shared their negative views or experiences about the health care service received. Similarly, interviewed healthcare professionals may not have shared their true practices if they were not perceived as a good practice, e.g. lack of patient involvement in decision making, not following local guidance or policies. To overcome this during the interview KM aimed to build rapport with participants by maintaining a conversational tone, responding to verbal and non-verbal clues, and inviting interviewees to further clarify or elaborate on provided responses with planned and un-planed follow-up questions. Also, KM kept a reflective journal to review the process and content of the interviews and to improve the quality of subsequent interviews. Several other mechanisms acknowledged to enhance credibility were also employed in this study: triangulation and peer review of findings (Mays and Pope 2000; Reynolds et al. 2011; Tracy 2010). Triangulation in the study was achieved by comparing the findings from three different participant groups (patients, healthcare professionals, key stakeholders) and collected routine documents. Although member checking was not employed in this study, the results were reviewed by the PPI Advisory group, the supervision team, and external research group members.

Dependability refers to the reliability and consistency of study findings that would be obtained if the study was repeated with the same or similar participants in the same
context (Lincoln and Guba 1985). Detailed methodology and systematic methods employed in this study ensured an audit trail of decision making during the conduct of the study. Also, the researcher's biases were acknowledged earlier in this Chapter and reflective journaling undertaken during data analysis to increase transferability of the study and its findings (Creswell 2013; Mays and Pope 2000; Reynolds et al. 2011; Tracy 2010) and thus improve the dependability of the research process (Moon et al. 2016).

Transferability refers to the degree to which the research findings are transferable to other settings or contexts (Lincoln and Guba 1985). Qualitative research does not aim to produce generalisable findings (Creswell 2013), and thus true transferability is not possible or desirable (Moon et al. 2016; Tracy 2010). Instead, transferability in qualitative research could be understood as the usefulness of the findings to other settings, populations (Tracy 2010), theory, practice, or future research (Moon et al. 2016). Thick and rich descriptions of the research setting and participants are provided in this thesis to enable readers to evaluate the applicability of the study findings to similar settings (Lincoln and Guba 1985; Mays and Pope 2000).

Confirmability is concerned with the researcher's objectivity during the interpretation of the research data (Nowell et al. 2017). The researcher (KM) might have influenced data analysis through her preconceptions (discussed in section 4.3.3) and potential greater focus on areas deemed important by her. To overcome this, KM kept a reflexive journal during the research process to record her impressions, thoughts, motivations, and biases about the studied phenomenon and collected data. The reflexive journal was regularly reviewed during data collection and analysis to increase self-awareness of its impact on data analysis and presentation and to ensure the study results were based on the perspectives of participants rather than the researcher. Moreover, the Framework method was employed which provided a clear audit trail to the analysis process and the supervision team was involved in the process to minimise the researcher’s biases.

4.9 Regulatory and ethical considerations

This section provides an overview of regulatory approvals obtained. It also describes processes followed to ensure the research was conducted in an ethical way, and anonymity of participants was protected.
4.9.1 Regulatory approvals

This study was conducted within the NHS and involved patients and NHS staff. Therefore, it required the Health Research Authority (Appendix T) and NHS Research Ethics Committee (Appendix U) approvals. A non-substantial amendment was obtained to include interviews over the phone in addition to face-to-face for healthcare professionals and key stakeholders (Appendix V). Additionally, approvals from CCGs and NHS Trusts at each health economy were sought. The researcher had an NHS contract, and thus access to the studied NHS sites was permitted through an NHS letter of access. Table 4.2 provides a summary of approvals.

Table 4.2 Summary of research approvals sought and granted.

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</tr>
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4.9.2 Ethical considerations

The risk to patients in this study was deemed to be low. The research involved patients with a long-term condition, i.e. AF, who were mainly older patients with or without other comorbidities. Patients were recruited from primary care and secondary care outpatient clinics with the likelihood that their condition was stable. The researcher advised three patients to contact a relevant healthcare professional at the end of the interview as they wanted information about DOACs. It was in line with the research protocol. None of the patients were identified to be at risk based on information they disclosed during the interview, e.g. the participant was not taking their prescribed medicines. No other risks were identified to participants.
The participant burden was also judged to be low. Participants took part in one interview. The interview was arranged at the time and place convenient to the participant.

Informed consent was obtained from all study participants. All participants received a participant information sheet. The researcher explained the study in detail and answered any questions a participant had. Participants had at least 48 hours to consider whether to take part in the study. Written informed consent was obtained from all participants before the start of the interview.

The researcher told participants that the interview could be stopped for a break or altogether if needed. Two participants required a break in the interview to answer a phone call. None of the participants became upset about their experiences during the interview.

Participants were able to withdraw from the study up to two weeks after the interview (before data analysis). The research protocol stated that the participant would contact the researcher. Then the researcher would securely destroy all data collected from the participant and not use it in the study. Withdrawal, after data analysis had taken place, was not permitted. None of the participants withdrew from the study.

4.9.3 Data security

The researcher followed the requirements of the General Data Protection Regulation, Data Protection Act 2018, and the NHS Code of Confidentiality with regards to the collection, storage, processing, and disclosure of personal information. The minimum personal-identifiable information possible was collected during the study. All research generated data were securely stored on a secure password protected server and computer at the University of Bradford.

The audio records of interviews and subsequent interview transcripts were assigned a unique identifier code generated by the researcher. Identifiable information (e.g. names, places) mentioned in the audio records were removed from the interview transcripts, i.e. transcripts were pseudo-anonymised. A look-up table was created by the researcher to link identifiable information about participants to their pseudo-anonymised records. Identifiable and pseudo-anonymised data were stored separately. Although the names of organisations were not used in the thesis and
publications, studied organisations could be identified from the context. It was highlighted to participants during the informed consent process.

The researcher deleted the audio records of interviews from the voice recorder after the transfer to the server was completed. Transcribing verbatim was completed by both the researcher and a professional transcription agency. The transcription agency used a secure password protected server to receive and send files. The agency received audio-record files with assigned unique identifier codes. The researcher deleted the files on the server after the transfer was completed. All transcripts were checked by the researcher for content accuracy and to ensure that identifiable information was removed.

Copies of paper consent forms were converted into a digital format. After the conversion, the researcher securely destroyed paper copies by shredding them. The researcher will delete all collected identifiable information, e.g. audio records, from the server within 12 months after completion of the PhD course.

**4.10 Summary**

This chapter has provided a detailed account of the methodology and methods employed to meet the aims and objectives of the research study. The philosophical perspective of critical realism, informing the research was explored alongside the Diffusion of Innovations in Service Organisations model that guided the research. Various data sources (non-participant observations, routine documents, semi-structured interviews) were used to collect the data. The data were analysed using the Framework Analysis method. The results of the data analysis are discussed in Chapter 5-6. Chapter 5 will present the results of interviews with patients taking an oral anticoagulant for stroke prevention in AF. Chapter 6 will present results of interviews with healthcare professionals and key stakeholders that were involved in the care of patients with AF or in the implementation of DOACs within the studied health economies.
Chapter 5 Factors affecting the uptake of new medicines: perspectives of patients

5.1 Introduction

A systematic review described in Chapter 2 highlighted that the influence of patients in the uptake of new medicines was relatively unexplored. The literature to date focused on how patients' demographic, clinical, and socioeconomic characteristics affect the use of new medicines. There is a lack of studies exploring how patient involvement in the decision-making about the choice of new medicines affected their use. The narrative review in Chapter 3 findings reported that patients with non-valvular AF had limited or no involvement in the decision-making about the choice of oral anticoagulant therapy. The notion of patients feeling that they were involved in the decision-making was visible only in quantitative studies when warfarin and at least one DOAC were available, and patients were offered a choice between them. Therefore, a qualitative study was undertaken to explore perceptions of patients with AF on the barriers and enablers to the uptake of DOACs and their involvement in the decision-making about oral anticoagulant therapy.

The methods used to recruit patients and analyse the collected data are described in detail in Chapter 4. In summary, recruited patients from primary and secondary care in three health economies were interviewed using a semi-structured interview guide. The interviews were undertaken between August 2018 and April 2019. The following sections of the chapter present characteristics of the interviewed patients, findings from the data analysis, a summary of the findings, and strengths and limitations.

5.2 Sample characteristics

A total of 21 patient were interviewed in the study (Table 5.1). Twenty-two patients expressed interest in taking part in the study, but one declined to participate due to feeling unwell after being contacted by the researcher. The age of participants ranged from 55 to 83 years, mean 72 years (standard deviation (SD)=8) and 76% were males. Slightly younger patients were recruited in the health economy B with an average age of 67 years (range 55-73; SD=8) compared to the health economy A participants with an average age of 74 years (range 58-82; SD=9) and health economy C participants with an average age of 74 years (range 65-80; SD=6). The ethnicity of all participants, except one, were White. Of 21 participants, ten patients were taking warfarin, six
rivaroxaban, three apixaban, one dabigatran, and one edoxaban at the time of the interview. Two patients taking a DOAC had previously taken warfarin and one patient experienced a switch between two different DOACs. The median (interquartile range (IQR)) time of taking oral anticoagulant was three years (four weeks - seven years), warfarin seven years (three - nine years) and DOAC one year (four weeks - four years).

The conducted semi-structured interviews were face-to-face and lasted between 15 and 48 minutes (average 27 minutes).

**Table 5.1 Demographics of interviewed patients.**

<table>
<thead>
<tr>
<th>Participant name*</th>
<th>Health economy</th>
<th>Sex</th>
<th>Age</th>
<th>Oral anticoagulant taken</th>
<th>Duration of taking oral anticoagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1-A-D</td>
<td>A</td>
<td>Male</td>
<td>58</td>
<td>rivaroxaban</td>
<td>2 years</td>
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<tr>
<td>P2-A-W</td>
<td>A</td>
<td>Male</td>
<td>83</td>
<td>warfarin</td>
<td>15 years</td>
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<tr>
<td>P3-A-W</td>
<td>A</td>
<td>Male</td>
<td>65</td>
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<td>6 years</td>
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<tr>
<td>P4-A-W</td>
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<td>Male</td>
<td>70</td>
<td>warfarin</td>
<td>8 years</td>
</tr>
<tr>
<td>P5-A-W</td>
<td>A</td>
<td>Male</td>
<td>81</td>
<td>warfarin</td>
<td>23 years</td>
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<tr>
<td>P6-A-D</td>
<td>A</td>
<td>Female</td>
<td>82</td>
<td>rivaroxaban</td>
<td>4 years</td>
</tr>
<tr>
<td>P7-A-W</td>
<td>A</td>
<td>Male</td>
<td>76</td>
<td>warfarin</td>
<td>10 years</td>
</tr>
<tr>
<td>P8-A-W</td>
<td>A</td>
<td>Male</td>
<td>78</td>
<td>warfarin</td>
<td>3 years</td>
</tr>
<tr>
<td>P9-B-W</td>
<td>B</td>
<td>Male</td>
<td>64</td>
<td>warfarin</td>
<td>3 years</td>
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<tr>
<td>P10-B-W</td>
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<td>Female</td>
<td>55</td>
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<tr>
<td>P11-B-W</td>
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<td>Male</td>
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<tr>
<td>P12-B-W</td>
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<td>Female</td>
<td>69</td>
<td>warfarin</td>
<td>9 years</td>
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<tr>
<td>P13-B-D</td>
<td>B</td>
<td>Male</td>
<td>73</td>
<td>edoxaban</td>
<td>3 weeks</td>
</tr>
<tr>
<td>P14-C-D</td>
<td>C</td>
<td>Female</td>
<td>79</td>
<td>apixaban</td>
<td>2 years</td>
</tr>
<tr>
<td>P15-C-D</td>
<td>C</td>
<td>Male</td>
<td>72</td>
<td>rivaroxaban</td>
<td>4 weeks</td>
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<tr>
<td>P16-C-D</td>
<td>C</td>
<td>Male</td>
<td>65</td>
<td>apixaban (previously rivaroxaban, warfarin)</td>
<td>4 weeks</td>
</tr>
<tr>
<td>P17-C-D</td>
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<td>Male</td>
<td>65</td>
<td>rivaroxaban (previously warfarin)</td>
<td>1 year</td>
</tr>
<tr>
<td>P18-C-D</td>
<td>C</td>
<td>Female</td>
<td>75</td>
<td>dabigatran</td>
<td>5 years</td>
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<tr>
<td>P19-C-D</td>
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<td>Male</td>
<td>80</td>
<td>rivaroxaban</td>
<td>5 years</td>
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<tr>
<td>P20-C-D</td>
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<td>Male</td>
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<td>rivaroxaban</td>
<td>10 weeks</td>
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<tr>
<td>P21-C-D</td>
<td>C</td>
<td>Male</td>
<td>77</td>
<td>apixaban</td>
<td>8 weeks</td>
</tr>
</tbody>
</table>

Notes: *Participant name included patient number (e.g. P1), health economy the patient was from (A, B, or C), and oral anticoagulant taken (W: warfarin or D: DOAC).

**5.3 Framework analysis results**

Interviewed patients recalled their experiences of consultations when oral anticoagulants were started, their involvement in the decision-making, therapy choices offered, and experience with the prescribed oral anticoagulant therapy. Patients also discussed their preferred consultation style, factors affecting patient involvement in the decision-making, and the use of new medicines. Four themes with 11 subthemes were developed during the analysis (Figure 5.1). The themes and subthemes are discussed...
in detail in the following sections and supported by representative quotes from participants.

Figure 5.1 Summary of developed themes and subthemes from the interview data with patients.

5.3.1 Limitations of NHS resources

This theme presents patients' views about NHS resources, specifically limitations of these resources, and how it affected the choice of oral anticoagulant therapy they were offered. The theme is presented in three subthemes: medicine cost considerations, consultation time constraints, and varying local services.

5.3.1.1 Medicine cost considerations

This subtheme presents patients' views on how the cost of medicine affected the choice of oral anticoagulant offered to them during their consultations. Many interviewed patients perceived DOACs to be more expensive than warfarin, an established therapy. They thought that cost of medicine influenced prescribers' decisions on which oral anticoagulant they were offered and prescribed during consultations. Patients expected a medicine perceived to be cheaper, i.e., warfarin, to be favoured over DOACs by clinicians. Indeed, some patients were told by their clinicians that cheaper medicines were used first and more expensive medicines like DOACs reserved as a second-line option if warfarin did not work.
“I asked my GP why I have been prescribed this medication [warfarin], I hear there is another medication that does not require a blood test, does not require as long as we take one every day that’s it. He [GP] says we start you with warfarin because it is affordable by [the] NHS, but if the [warfarin] clinic says to you, you are not getting the level we are looking for, we can prescribe another medication which one tablet without any test … he was clearly saying we always start with warfarin because it is affordable, the other medication they are costly.” (P9-B-W)

Some patients also questioned if warfarin was indeed a cheaper option than a DOAC. These patients were started on warfarin and discussed costs associated with warfarin monitoring, such as healthcare professionals’ time and monitoring equipment. Although a DOAC was perceived to be more expensive than warfarin, they thought associated costs with warfarin monitoring made warfarin more expensive in the long term. Some patients even suggested that the use of DOACs would help the NHS to save money by releasing staff from warfarin monitoring clinics to see other patients. Also, one patient who started on DOAC therapy was told by his doctor that the cost of a DOAC was similar to warfarin due to the lack of required monitoring.

“The cost will be lower [of a DOAC] because the productivity will be more … this is [warfarin] costing NHS plenty of money because when I go to the clinic, I am using the time of the secretary, I am using the time of the nurse, I am using the material for checking, I am using the device, I am using the paper, I am using the time of the nurse or the pharmacist, all that is recovered from the time of … for the cost of this. For me, I just thinking about, okay, I am having every three weeks going to speak with nice people, checking my condition - that’s fair enough but is this looking right by the NHS? No, I don’t think [the] NHS [is] helping themselves prescribing this medication [warfarin] while if they prescribe these medications [DOACs] will require only to take it once and forget about it, they will save more than the money they save from prescribing [warfarin].” (P9-B-W)

Patients rationalised the use of cheaper medicine by discussing the NHS financial budget. Many interviewed patients were acutely aware that the NHS has a limited financial budget and needed to continually try to save money, including its expenditure on medicines. Hence, patients accepted the preference to use less expensive medicines as a standard practice within the NHS.
“I mean they [NHS] are very sensitive to cost, aren’t they? If you can save a bob, save it, I understand that because they are always strapped for cash.” (P11-B-W)

Other patients acknowledged not knowing what their medicines cost and thought it had no impact on their doctor’s prescribing decisions. Despite being aware or not of medicine cost, some patients were not concerned that a cheaper oral anticoagulant was favoured as long as it was working in preventing AF-related stroke. Furthermore, a few patients viewed taking cheaper medicine as a way of helping the NHS.

“I don’t mind help the NHS to take the cheaper medication as long as it is going to do the job.” (P9-B-W)

However, not all patients were happy with the cost being prioritised in making therapy decisions. They wished therapy options were tailored to their needs by considering their health status, lifestyle, and preferences. They wanted what was the best for them and not necessarily for the healthcare system, e.g. meeting cost-saving targets. As such, some patients were willing to pay for the new, more expensive medicine if it meant a better quality of life. However, not all patients could afford private healthcare and thus rely on what was offered by their clinicians.

“I think the key point is there may be something better for me and I want to have that discussion and if somebody said to me, ‘Well you know we can’t afford it on the NHS’, well fine I’ll pay for it privately. I don’t mind, if that gives me something a lesser risk, a better lifestyle because to me it’s not the longevity it’s more about quality.” (P3-A-W)

“You are rich they’ll buy the one they want, the one they need and rest of the peasants like me will get what we’re given.” (P5-A-W)

Also, some patients expressed frustration with the control of the spending on medicines as they perceived money being wasted in other areas of the NHS. They argued if the wastage were prevented, the NHS would not need to restrict the use of more expensive medicines to patients.

“As long as it’s not leaking money that would be … as far as cost goes if they could just concentrate on where the money is being leaked, and it is being leaked, you know doubling up on tests where they don’t need to be done … Why does a blind in a ward that needed to go up cost something like £400-£500 when it could have been got for £50 because they have to use a certain supplier, why? Somebody is making money.
Now that frustrates me in the NHS and the cost because it is difficult for the drugs isn’t it?” (P12-B-W)

5.3.1.2 Consultation time constraints

Patients discussed the constraints of consultations in the context of limited time and NHS financial and workforce resources. Many patients, when starting anticoagulation, stated the standard ten minutes allocated to a consultation with a GP was not enough to discuss therapy options. As a result of time constraints, clinicians were perceived to make decisions quickly and had no room for discussion with a patient.

“Well, if the doctor was going to sit and offer me options and discuss the pros and cons of the various medicines which might be available, then a 10-minute appointment isn’t going to cut the mustard is it?” (P18-C-D)

“I think patients do need to be given a choice and spent time with, the problem is decisions are often made quickly ...” (P10-B-W)

Some patients thought that asking for an explanation about medicines was wasting doctors’ time, and thus patients should not expect it. They feared becoming a burden to the system that was perceived to be already under pressure and some did not feel empowered to do so. Instead, patients thought they should "rely on the doctor to choose what's right" (P5-A-W).

“You know the health service is under a great deal of stress at the moment, I’m okay I’ve not died yet, I don't have anything that’s affecting my lifestyle that I need to go back seeing the doctors. Therefore I don't go back, I'm not going to knock on his door and say I want this or I want that, I want that or whatever else. So no I don't feel empowered to do that but I'd like to be.” (P3-A-W)

Other patients suggested that longer consultations were needed for doctors to explain available therapy choices and hence involve patients in the decision-making process. Some patients also commented that receiving information leaflets was not enough as they needed explanation from the clinician to understand it. However, some patients were clear that having an extended consultation was not possible due to the NHS being short of qualified personnel and overwhelmed with patients. Patients thought that additional time in consultations and the provision of printed leaflets would require additional money that the NHS did not have. One patient also believed that some patients from minority ethnic communities in his area did not speak English. In his
view, these patients would need an interpreter in consultations for all available options to be explained, hence increasing spending in the NHS.

“It [shared decision-making] is going to cost the NHS a lot more, isn’t it? Because it is going to be time, it is going to be printed leaflets …” (P18-C-D)

Also, patients taking warfarin thought that being informed about alternative therapy options once already taking an oral anticoagulant would not be realistic due to consultation time and financial constraints of the NHS. Hence, both patients and doctors prioritised resolving symptoms presented by patients rather than improving what was perceived as already working in consultations. Consequently, some patients were of opinion that patients who already take warfarin without problems would not be told about alternative therapy options, i.e., DOACs.

“If you went to inform the people on warfarin about a new one where would you get your millions from, it would be a very expensive procedure … If you were offering them a choice of three you would need to give them the information again cost … I mean if you have gone with something I don’t know pain within your stomach, you’re not going to be bothered about talking about the possible improvement you get from something else if it was going to detract from why you had gone …” (P5-A-W)

Despite consultation constraints, some patients discussed work-around strategies. For instance, some patients booked two appointments instead of one with their GP. Thus, they had 20 minutes to discuss their condition.

“Our doctor’s appointment is 10 minutes, 20 minutes if you book it if you say you want a double …” (P5-A-W)

Some patients also experienced a variation of consultation time between different GPs. In some cases, patients were not restricted to 10 minutes and were given the time they needed to discuss their condition during the consultation. Therefore, they did not think that allocated time to consultations affected the choice of oral anticoagulant prescribed. Whereas, other doctors were strict with appointment times and finished consultations when 10 minutes were up. The varied approach by GPs to consultations concerning their length also led to longer waiting times and appointments being late. However, patients thought that was a part of the process that they needed to accept.
“They say it’s 10 minutes per patient. I mean I can go up to the doctors ... I can be waiting an hour before I even go in. I think as timewise, as I say, all doctors are different. Some doctors like the doctors up there [his GP practice], a couple of them up there, I'll go in there and I'll sit, and they'll talk and talk until I'm ready to go. You have got another doctor who will be in there and is precise. In blah, blah ... and you are out. You are out in your 10 minutes.” (P20-C-D)

Some patients also indicated a difference between consultations experienced at the GP practice and the hospital outpatient clinic. The latter offering more time to have an in depth discussion, whereas GPs were perceived to have no time for longer conversations due to their high workload.

“I think the workload tends to get in the way [for GPs]. Don't get me wrong you know they can only prescribe on the information that you will give them, so they have got to go with that but as for a hospital it's more in-depth ...” (P21-C-D)

5.3.1.3 Varying local services

When discussing barriers to the use of new medicines, some patients questioned if established local services could dictate what medicines were offered to patients. For instance, one patient speculated that only warfarin was offered to them because there was an established warfarin clinic at their GP practice.

“Also you get the feeling why wasn’t I offered the new stuff ... was it because there is a very well established warfarin clinic at the practice every Friday and it's easy just to work with one drug rather than four, I don't know ... and more you know we've done this, this is how we do things here, it's warfarin and warfarin only right now ...” (P3-A-W)

Another patient gained the impression from their conversation with their GP that the warfarin clinic at a hospital rather than the GP or the patient made the decision which oral anticoagulant to use.

“It's not up to you, it is up to the clinic, if the clinic they see that warfarin doesn't work for you then they will go and give you, they advise you to all different medication.” (P9-B-W)

A few patients wondered if, in the area they live, only certain medicines were available. For instance, one patient recalled their previous experience with the NHS of availability
of service depending on their geographical location. They thought that might apply to the availability of new medicines, including DOACs, as well.

“My daughter had cancer. Now when we applied for a wig, because of our postal code, she wasn’t allowed that on the National Health. But if I had gone over to the other side of town, she was allowed the wig. And that is exactly the same with medicines, isn’t it? And some of it, whether that’s true or what I don’t know on costing and your postal codes again if it is depending on which postal code you’ve got you get a dearer medicine because there are cheaper medicines and dearer medicines isn’t there? And I don’t really know. So, it is a, we won’t ever get to know that. That’s up to the practice that organises it you know what I mean?” (P13-B-D)

Also, one patient considered a theoretical possibility of incentives to prescribe a certain medicine but was reluctant to suggest that was the case in her experience.

“Well I don’t want to …, I mean I suspect …, I mean I don’t know whether people benefit from prescribing one, I don’t know. I mean, that is a theoretical option, isn’t it, but I wouldn’t for one moment suggest that it was the case.” (P18-C-D)

5.3.2 Clinician-patient encounter

This theme describes patients’ experiences and views on their interactions with the clinician and how it affected their involvement in the decision-making about the choice of the therapy. The theme is presented in three subthemes: perceived roles, relationship continuity, and prescribing habits.

5.3.2.1 Perceived roles

This subtheme presents patients’ views and reasoning on their and clinicians’ perceived roles in consultations. Some patients perceived their role was to tell their symptoms and follow the clinician’s instructions. At the same time, it was the doctor’s role to make therapy decisions.

“You tell them what’s the matter with you, and then they tell you whether they look at their monitor thing in front of them. And then they come up with some ‘You ought to be on such and such or do such and such or whatever. And I say ‘Fine, right good afternoon,’ come out. I only tell them if something’s wrong.” (P6-A-D)

Some patients reflected that they were brought up to accept doctors’ authority and follow their instructions “like a good patient”. In their view, this is how the NHS works
with the doctor making decisions. Furthermore, a few patients commented that being involved in the decision-making process had never occurred to them.

“I'm a bit old in the tooth for that. I've been brought up like that that you do as you're told for doctors tell you and you know.” (P6-A-D)

Some patients also revealed that they did not ask questions during consultations. A few patients suggested that questioning the clinician indicated a lack of respect. Also, some patients said that they were not asked about their therapy preferences or opinions.

“I think it's the history of how the NHS works, I think they're being very much a doctor this, doctor that, doctor says you should do so and so, oh right so you do it. The doctor says chop my hand off, okay, you know. People are not used to asking doctors questions or question that doctors might not be right. Nor am I.” (P11-B-W)

Others viewed that there was only a choice between accepting or refusing the anticoagulation. Patients accepted the therapy to prevent their condition from deteriorating, having a stroke or even death. Hence, some patients thought that there was no need for their involvement in the decision-making, especially when only one therapy option was presented.

“It was that [warfarin] or nothing, on or off. I could have said yes and no, well yes or no did I want it or not, but it would be crazy not to go onto it.” (P3-A-W)

Furthermore, a few patients said that involving patients in decisions could cause anxiety, confusion, or overload them with information. For instance, one patient described seeing a consultant as a “nerve-wracking” experience on its own and could not think about making therapy decisions. Moreover, another patient thought that patients voicing their therapy preferences would negatively affect clinicians’ prescribing options and put patients’ health at risk.

“I think there's a potential to have too much of a role so, you know, you're dictating to the doctor and the doctor's having to meet the personal needs of the patient rather than the medical needs and I think that puts a danger that might inhibit the doctor then when prescribing things.” (P4-A-W)

Patients believed and expected that doctors would make the best and right decision tailored to their needs and circumstances. Additionally, some patients had a positive
experience with the lack of involvement in past consultations. Hence, these patients put their trust in the clinician, were happy with the doctor's prescribed therapy, and little or no involvement in deciding on the therapy choice. These included patients started on either warfarin or a DOAC.

“You would rely on the doctor doing the best for you basically and there should be no reason why you wouldn't, would you, why he would or she wouldn’t … I just accept that what they're giving you is in your best interest really.” (P4-A-W)

“I have been going to that surgery for lots and lots of years and I always find them very good, so I just accepted the fact that what they were telling me was the same, you know.” (P2-A-W)

In contrast, other patients experiencing no involvement in the choice of therapy wished they had an opportunity to discuss the therapy options, why they needed it, and its implications in more detail. This was particularly the case for patients who were unsatisfied with their current oral anticoagulant therapy, mostly warfarin. They reasoned that they should have a say in the choice of the therapy as they are going to have to live with the decision made. Furthermore, previous negative experience with lack of involvement in decision-making during consultations deterred patients from such consultations in the future, and they were more determined to be involved in decisions. As such, these patients preferred discussing with the clinician to make a joint decision.

“I like to be told you know these are the options, these are the pros, these are the cons … I like to be part of the decisions, I would prefer … where it’s almost a joint decision.” (P3-A-W)

Some patients who started on a DOAC experienced making the decision together with the doctor. They were given a choice between warfarin and a DOAC. Thus, they had an opportunity to voice their preferences towards the choice of oral anticoagulant. They also were more inclined to ask questions to start a discussion with the clinician, which was partially driven by the fear of potential medical mistakes. These patients were satisfied that the decision was made together with the clinician.

“We've both got a say, that's it discussed, you know, the pros and the cons for it and then you can put your point of view forward and the consultant put his and hopefully you'll come to some mutual agreement … I think it's much more beneficial for both
the consultant and myself to have a discussion about it and both decide which one might be best.” (P14-C-D)

Some patients also commented that communication in consultations between a patient and the clinician depended on the clinician they saw. Despite patients asking questions, some clinicians were perceived to ignore or were perceived to get irritated by them.

“I do ask questions, but quite often the doctor is concentrating on one thing that you’ve said and they ignore you, so you don’t get any questions [answered].” (P7-A-W)

Only two patients described choosing themselves which oral anticoagulant to start. One patient asked for time to read about available therapy options to make an informed decision in the next consultation. Whereas another patient was told by the clinician to make a choice. He was dissatisfied with the consultation as he preferred the doctor to make the decision.

“I asked the doctor if he had any preference. He said, "No and I can't offer you one", he said "It has to be your choice. So, I'd no alternative but to choose one of them you see. I had to make the choice. The doctor should have been making the choice in my opinion.” (P8-A-W)

Furthermore, some patients recalled being diagnosed with AF and started oral anticoagulant therapy during acute hospital admission. They described at the time of diagnosis feeling unwell and worried about their health and risk of having a stroke. They were concerned with surviving or getting better and were grateful for being looked after. Hence, in these circumstances, patients did not feel it was the right time for them to get involved in the decision-making about the choice of oral anticoagulant therapy, and they detached themselves from participation. However, a few patients reflected that they should have been more proactive in asking questions about the available therapy options.

“I was not well. I was too poorly. I was happy to be in there [hospital] receiving wonderful attention and I was getting some medication of what I needed … I know that anything blood going through the heart can result in a heart attack or stroke. So, I thought it's a blessing that I have been found out.” (P21-C-D)
Also, a few patients stated that acute hospital admission did not support patient involvement in the decision-making about oral anticoagulant therapy. They perceived that doctors were making decisions quickly to respond to their presenting symptoms in a timely way. Hence, there was no time to provide or ways for the patient to obtain information needed to consider different therapy options and take part in the decision-making process.

“A lot of time decisions are made very quickly without the patient having time to think about it adequately, because I certainly was in the hospital bed, couldn’t have looked up the information I wanted to look up for myself.” (P10-B-W)

5.3.2.2 Relationship continuity

This subtheme presents patients' perspectives on the relationship continuity with their clinician and how it affected their involvement in decisions about oral anticoagulant choice. Some patients described experiencing a lack of relationship continuity with their clinicians. They saw a different clinician every time they had an appointment at the GP practice.

“I mean you go in and I see names come up, and I haven't a clue who they all are, it's different doctors then next news they've gone, and there's somebody else up there.” (P6-A-D)

Patients indicated it was because of a high turnover of staff at their practice. As such, patients did not know the clinician they saw. They perceived that a new doctor did not know their medical history, which prevented being involved in the decision-making process or having enough support when choosing between oral anticoagulant options.

“If you get someone that you see on a regular basis, at the other place there was someone that is possibly your GP if he's not available, you see someone else, yes, when you see the same one he knows what you're doing, he knows your story a bit more than the other one, the other one is spending 10 minutes trying to read your information on the screen. So, the consultation is going to be 10 minutes, so at the end of the story, he just says, “Here, have this,” and he goes. Yes, obviously, it makes a difference.” (P17-C-D)

When asked, patients indicated that they prefer to see a regular doctor who knows them. Hence, they could develop a relationship with the clinician, ask questions, and consequently get involved in the discussion about available therapy options. However,
patients stated that trying to see the same doctor was challenging. Some of the patients accepted that it was not possible due to the large numbers of patients seen at the GP practice.

“I've just got a lot closer to a couple of doctors, well three doctors at the local surgery who seem to be taking more interest in that, so I have got to say that... So I think if I pushed for anything in terms of doctor consultation, I would push that you went to the same GP's all the time who knew what was wrong with you and had a personal interest in you if you like if you call it that.” (P4-A-W)

Only a few patients described seeing a regular doctor and experiencing good communication with them. For instance, one patient described receiving clinical letters after appointments with a specialist nurse at the hospital that were sent to his GP. The patient felt more in control of his health management and thus was able to ask his GP or the specialist clinician questions if the action in the clinical letter was not undertaken. Also, some patients who started on warfarin described building a relationship with the pharmacists at the warfarin clinic and being able to ask them questions and therefore becoming more involved in their management of warfarin.

“I get a regular consultation. The clinician that I see for warfarin at the GP came out one Saturday afternoon to see me because my reading wasn't right and that was giving up his own time I'm presuming … Right well, he obviously knows me, and he will make allowances. If the reading is out one week, he will certainly see me the following week and things like that, so I feel as though that is very well monitored, the warfarin in respect of my medication.” (P4-A-W)

A few patients described using a community pharmacy for additional advice or information as they had built a relationship with them. These patients valued their advice and perceived them to be approachable.

“I do speak to my pharmacist because I'm very friendly with him. It's actually in the doctor's surgery, and he is a nice man I spoke to him about things, and he's always advised me.” (P20-C-D)

However, other patients reported minimal input from community pharmacists and saw little value in medicine use reviews done in community pharmacy. They perceived that community pharmacists did not have access to their medical records and thus could not holistically review their medication.
“Every now and then you know whenever we go to collect medication from [the] pharmacy, and they review. They would say, are you good with your medication. But then again, they do not know what is what and just ask how you are getting on with your medication … I think they [medicine use reviews] are a waste of time because they do not know all the that a day before I have been to the hospital and had an ECG, blood tests. I think it is just that they have to do it now.” (P16-C-D)

5.3.2.3 Prescribing habits

This subtheme describes patients views on clinicians' openness to different oral anticoagulant options and its impact on deciding which oral anticoagulant(s) to offer patients and prescribe. Despite many patients seeing doctors as experts, some patients queried the knowledge and experience of prescribers that could potentially affect the use of new medicines. Some patients suggested that doctors might not be aware of the latest information about available new oral anticoagulant therapy options. Hence, patients were not informed about DOACs during their consultation, and the doctor did not prescribe them.

“It's probably the doctors not being up to date with what usage they [DOACs] are ... “ (P8-A-W)

Some patients suggested that some doctors' were unwilling to change their prescribing habits due to their familiarity with warfarin. They expressed the view that the established warfarin prescribing and monitoring service discouraged clinicians from considering using DOACs. Other patients perceived that doctors had their preferred oral anticoagulant as it was easier to learn and work with one rather than five different oral anticoagulants and that the preferred medicine was the one the doctor had the most knowledge about and experience with. Hence, patients viewed doctors being more comfortable with prescribing the established warfarin therapy.

“There is certainly from my experience this comfort with warfarin, it has been used, it has been tried, we have got dozens of patients on it, we have a system set up to monitor it ...” (P3-A-W)

A few patients suggested that the unwillingness to change their prescribing habits was linked with the age of the clinician. Older clinicians were perceived less likely to change their prescribing practice to include DOACs. Instead, they were seen to continue using warfarin, which has been in practice for many years.
“Because some places the doctors they are flipping old … and that err … I don’t … I don’t think some of them want to pick up new about new read about new pills … some of them are stuck in the past.” (P1-A-D)

However, what patients were offered during the consultation was also influenced by prescribers' views on individual oral anticoagulants. For instance, most of the patients initiated on DOAC therapy were told by their doctors that it was better than warfarin.

“I asked if it was like warfarin, but he said no … that's old fashioned or something, they don't use it as much now because they find that these are better or something.” (P15-C-D)

5.3.3 Oral anticoagulants knowledge

This theme considers patients' knowledge about oral anticoagulant therapy options and how it influenced their preferences of the therapy. The theme is presented in three subthemes: awareness of therapy options, safety concerns, and effectiveness.

5.3.3.1 Awareness of therapy options

This subtheme describes patients' awareness and knowledge of oral anticoagulants and how it affected their choice of therapy. Before the initial consultation, some patients were already familiar with warfarin. They learned about it from their social (e.g. family, friends, acquaintances) and professional (e.g. working in healthcare) networks.

“I knew about warfarin before because I knew from acquaintances who were on warfarin and what it involved.” (P18-C-D)

Some of these patients were involved in the decision-making about the choice of oral anticoagulant and used prior knowledge to inform their decisions and preferences. For instance, one patient selected warfarin rather than a DOAC due to being familiar with it. Whereas another patient selected a DOAC because warfarin was seen as a burden to his family member taking it. Relatively few patients knew about DOACs before their consultations.

During a consultation, many patients on warfarin and some on DOAC therapy said they were not given a choice and told only about one oral anticoagulant. Some of these patients did not expect doctors to tell them about different available options because in their experience doctors do not discuss treatment options. For instance, one patient
commented that he would more likely learn about new medicines from his social network rather than from his doctor.

“Probably the atrial afib group [patient support group], I would get to know there. I don’t think the doctor would tell me, he’s never discussed anything like that with me, none of the doctors do.” (P7-A-W)

Many patients also discussed their lack of or limited knowledge about therapy options, the condition, and what was happening with them, preventing them from being involved in the decision-making. These patients relied on the doctor’s expertise and did not question the therapy choice made.

“I mean you can’t sort of go to a doctor and start talking about something that you know very little about and have only heard just once you know.” (P2-A-W)

Another patient taking warfarin expressed frustration that the medicine reviews he received focused on warfarin monitoring and reinforcement of information about it. However, these reviews did not include discussion or information about alternative oral anticoagulant options such as DOACs. Hence, he was not aware of DOACs and believed he was not enabled to consider switching from warfarin to a DOAC therapy.

“I get a nurse, a practice nurse who really just reviews and tells me what I’m on and what they do and I’m like yes I know that I can read about that or whatever else but there’s no dialogue at all about changing or improving or how I am they seem just to be looking at the coagulation factor or whatever it’s called, and that’s it.” (P3-A-W)

After the consultation, some patients were referred by their GPs to a local patient support group. They were able to discuss unanswered questions, experiences with prescribed therapy, and share information about AF and oral anticoagulants. Other patients looked for additional information about the prescribed medicines and alternatives. Patients who were experiencing issues with warfarin sought information about alternatives to warfarin from newspapers and news, family or friends with medical education or taking an oral anticoagulant, and the internet. Some patients said they wished they had been told about DOACs during their consultation because DOACs might have been better for them than warfarin. The newly acquired knowledge about DOACs and support from peers at the patient support group motivated some patients to ask their clinicians about the possibility of changing from warfarin to a DOAC therapy.
“As I say just literally searching online and looking at, you know, what was recommended for blood thinning … you think do I really want to be taking that sort of stuff [warfarin], isn’t there anything better really, hasn’t science brought anything else?” (P3-A-W)

“When I left the hospital, I have my younger brother who is a consultant orthopaedic, he was thinking well they might prescribe warfarin or some other medication where you don’t need any testing. So I was waiting for the hospital to send me an appointment. Then I went to the hospital, straight away they asked me to go to warfarin clinic … I didn’t challenge it and when I had the problem to get it right [INR] when I asked my GP [about the alternative to warfarin].” (P9-B-W)

A few patients said they were not interested in learning about other therapy choices. They were satisfied with their prescribed therapy. They thought that the currently prescribed oral anticoagulant was working well for them, and no change was needed.

“Warfarin is doing that for me so why would I change it? I’m inclined to say that if it’s not broken don’t try to mend it and as far as I’m aware warfarin’s working so I’d leave it alone.” (P4-A-W)

5.3.3.2 Safety concerns

This subtheme presents patients’ concerns about the safety of new and established oral anticoagulant medicines and how these concerns affected their preferences. Patients discussed how taking an oral anticoagulant was a significant part of their life and were concerned about possible side effects from them, e.g. bleeding. The patients interviewed accepted that all medicines have side effects but would prefer a medicine with less severe or more manageable ones. Most patients sought information about a medicine’s side effects profile, and some compared the side effects of warfarin and DOACs when making therapy choices. For instance, one patient declined a DOAC due to a side effect of dizziness, which could exacerbate her current complaint.

“If there was an alternative medication which has less potentially bad side effects, I would obviously go for it.” (P11-B-W)

Several patients voiced concerns about the unknown side and long-term effects of DOACs as they were new medicines compared to warfarin. In contrast, warfarin was perceived to be a well-tested medicine with established side and long-term effects and thus a safer option than a DOAC. The fear of the unknown led some patients to choose
warfarin over a DOAC. Also, some patients thought doctors started warfarin because they were also concerned with the safety of new medicines.

“[I] knew people that had had it [warfarin] at some time or another, so I opted for that as perhaps the safer option … warfarin has been around a long time; it must be reliable. The other one, I have never heard of it, do not know how long it has been around, got to be suspect.” (P8-A-W)

“Patients are fearful what the long-term effects are because of course with a new medicine you have no idea what is going to happen in ten years’ time.” (P14-C-D)

In contrast, some patients viewed DOAC as a safer option due to themselves or people in their social network experiencing side effects with warfarin, e.g. bleeding. The side effects experienced were linked to the safety concerns they expressed about warfarin therapy and even led to non-adherence in some cases. For example, one patient experienced tiredness and attributed it to warfarin and hence discontinued taking it. Some patients questioned the safety of warfarin due to its negative connotation of being developed initially as a rat poison. One patient associated warfarin with dying people. Another patient was worried about having regular blood tests required with warfarin monitoring due to the risk of contracting an infection. Hence, these patients perceived DOAC therapy to be a safer option.

“There were one or two people at the gym that have got exactly the same thing … they have had one or two side effects with the warfarin … with heavy bleeding and stuff like that. And I thought well I do not want that really.” (P18-C-D)

“You don’t know maybe one of these pricks I can get like one of these diseases … maybe one small mistake can ruin my life.” (P9-B-W)

The possibility of side effects with new medicines was not a worry for all patients. Some patients admitted not knowing the side effects of oral anticoagulants nor reading patient information leaflets. They assumed that the prescribed medicines were safe. Other patients were willing to try a new medicine with the possibility of improving their health or helping the healthcare team to learn more about a new medicine. They thought if they experienced a side effect, they could stop and change it to an alternative oral anticoagulant.
“The doctor would say ‘This is a new medicine, try it and we will see how it goes.’ I mean things like that are not irreversible are they, you can stop using them straight away if they are not having the effect or having an adverse effect.” (P4-A-W)

Some patients thought it was necessary to have frequent monitoring with DOACs to ensure the safety of the therapy. Many patients were aware or experienced frequent monitoring with warfarin, which gave them the feeling of safety, comfort, and being looked after. Hence, they had expected the same level of monitoring with DOAC therapy. Patients had concerns and a lack of understanding about infrequent or no monitoring associated with DOAC therapy. These concerns were further amplified by patients' perception that doctors had a lack of understanding about it too. Consequently, these patients felt warfarin with associated frequent monitoring was a safer option.

“So that [monitoring] is what swayed me to keep taking warfarin, because I mean it is quite a serious thing to be taking isn’t it, you know, a blood thinner … I think it is a bit dodgy if they are going to give you a tablet, though, and never call you back. I mean, I do not know that they do or not, but from what I understand, they set you up on it [DOAC], and that is it. I do not know when they see you again, if at all. Nobody seems to know. How do they know the dosage is right? I would probably feel safer with the warfarin knowing I can go and let them check it.” (P7-A-W)

5.3.3.3 Efficacy

Some patients talked about the effectiveness of oral anticoagulants. Patients agreed to take an oral anticoagulant to prevent AF-related stroke. They wanted to be informed about new medicines as they could be better and more reliable than their currently prescribed oral anticoagulant therapy. Many patients did not question the effectiveness of either DOAC or warfarin therapies. However, one patient said he would need more information about a new medicine for assurance that it would be effective in his age group before consider taking it. Whereas, another patient thought a new medicine would have more research evidence to show its effectiveness compared to old medicines and therefore was happy to take it.

“If there’s been plenty of people actually got benefit from it and I could be furnished with the volume of information showing that it is beneficial for old goats like me, then
I would say ‘Yeah give it I have a try at that, 'cause it's me that's going to have the stroke if these things don't work and strokes we do not want.” (P8-A-W)

Also, some patients prescribed DOAC therapy looked for assurance that the prescribed medicine was good by searching for information on the internet or consulting with their community pharmacist.

“I just said to him [pharmacist] 'what's with this rivaroxaban they've put me on. Is it good?' and he told me. He said, 'No, it's very good. It's a new one compared to the warfarin,' he said … I was happy enough to take it.” (P20-C-D)

Overall, patients perceived both warfarin and DOAC therapy to be effective, and hence efficacy had minimal or no influence on patients' choice of oral anticoagulant.

5.3.4 Impact on daily life

This theme describes the impact of taking oral anticoagulants on patients’ daily lives and how it affected their preferences for an oral anticoagulant. Patients wanted to choose a medicine that had simple dosing regimens, were compatible with their lifestyle and did not reduce their quality of life. It is presented in two subthemes: lifestyle changes and monitoring and dosing changes.

5.3.4.1 Lifestyle changes

Some patients on warfarin reported adjusting their lifestyle to fit with the medicine prescribed. Patients taking warfarin were aware of certain foods interacting with warfarin and thus adjusted their diets, e.g. reducing intake of vitamin K rich foods or alcohol.

“I am taking medication; I am adjusting my lifestyle to go with the medication.” (P9-B-W)

The impact of the adjustments required varied between patients. For some patients, it caused no difficulties, and they were happy to continue with warfarin. Some were also told by their clinicians that warfarin will be adapted according to their diet instead of patients needing to change their diets. Consequently, the explanation allowed them to continue with their desired diet and made the idea of taking warfarin more feasible and less disruptive to their lifestyle.

“We’ll fit the warfarin around you rather than the other way around and I think that made a significant difference to how you approach taking it and it’s not going to rule
your life and you can live a normal life without worrying about having to be tested all the time.” (P10-B-W)

Other patients described that warfarin caused issues due to their changing diets and travelling abroad. Thus, they were less satisfied with the therapy. A few patients described how they worked with their healthcare professionals to fit warfarin with the changes in their daily lives. For instance, one patient described how, together with the clinicians, they agreed on warfarin monitoring and dosing to manage changes of circumstances such as taking a course of antibiotics, fasting, or when going on holiday. A few patients described changing their holiday plans because of warfarin, e.g. shorter duration, no travel abroad.

“Every time before I go on holiday I inform them so we will … try to do a test just before my holiday and test after the holiday … so always they make sure that my holidays are very limited but when I go abroad … when I fast, I tell them this is fasting month and my diet will be completely different, I will be not eating and drinking for 18 hours, 17 hours, so they are aware of that and they try to make an appointment as a prior or after that change of my circumstances.” (P9-B-W)

Other patients refused warfarin due to the required change in lifestyle and were started on DOAC therapy instead. They declined warfarin as it was perceived not to fit with their lifestyle, e.g. frequent travelling abroad.

“Although I was retired, and I was about 70, I was still working and travelling, and it [DOAC] suited my lifestyle … had he put me on warfarin, I would have had to go every month for check-ups, and that would have seriously interfered with my lifestyle.” (P18-C-D)

Patients taking DOACs described minimal to no impact on their lifestyle. They took the prescribed medicine, did not need to have frequent monitoring appointments or change their diets.

“I just take one a day, and I do not bother. I think even they do not bother me.” (P6-A-D).

5.3.4.2 Monitoring and dosing changes

Patients described the impact of required monitoring and resulting in dose changes. As with the impact on lifestyle, patients taking DOACs described minimal to no impact.
Whereas, the impact of the adjustments to daily lives varied between patients taking warfarin. Some patients had no issues in attending warfarin clinics but acknowledged that their situation might change in the future, for example, a change in job or health status, and they would need to reconsider their oral anticoagulant therapy options.

“If my work changes and I need to have like leave to go to the hospital I would say no, this is not working for me, but at the moment with my circumstances, I can control my time, I have no problem.” (P9-B-W)

Some patients who were started on warfarin without having a different option presented thought doctors did not consider their circumstances when making prescribing decisions. These patients had challenges getting to the warfarin clinic due to lack of their own transport, reduced mobility, or unable to take time off work and therefore missed some of their appointments.

“The only downside is that I don’t know if you know the area, but where the doctor’s surgery is, it’s at the top of a massive hill, and I have to walk up there because I have no transport, and there is no bus.” (P2-A-W)

Also, some patients described occasionally forgetting to take the correct dose or missing a dose of warfarin, particularly as the dosing regimen frequently changed. The challenges with warfarin therapy encouraged some patients to enquire about alternative options.

“I was taking warfarin, and I was to go in every month to have the blood test and then have a different dose. There were like millions of bloody tablets because I used to take like three single ones, two of these, one of that, just I could not even remember them.” (P17-C-D)

However, some of these patients were told they were not suitable or could not have DOAC therapy. Hence, they discussed strategies to lessen the impact of warfarin on their daily routines. A few patients considered the possibility of self-monitoring at home to further reduce the burden of travelling to warfarin appointments. They were aware that it was possible but said that they were not offered or allowed it. Others asked for monitoring to be done closer to their home, e.g. at a local GP practice.

“Well, originally I was going to have to go to the hospital, I was going to have to go to [hospital], and that involves two processes in the hospital, you go into like a waiting
room and have these machines that issue a ticket number, and then you get the blood taken and what have you and then you have to go elsewhere as well, it's like a two-part one and very time consuming, so I asked if they could do it at my local doctors and they said 'yes'.” (P2-A-W)

Some patients described that they had developed strategies to remember to take warfarin at the correct dose by using prompts, such as their yellow warfarin booklet or application on their mobile phone.

5.4 Summary

The findings from interviews with patients provide important insights that could enable care providers to improve AF stroke prevention care. Whilst this section summarises the findings, the full discussion of the results is presented in the Chapter 8.

While there was a wide range of experiences and views, altogether patient narratives reveal a number of important factors for clinicians and others involved in patient care to consider. Altogether these factors influenced which oral anticoagulant therapy options were presented and prescribed to patients and consequently influenced patients' satisfaction with the prescribed therapy. The findings presented in this chapter are summarised below and the discussion of the findings is presented in Chapter 8.

The findings indicate that barriers to DOAC use were often linked to a lack of patient involvement in decision-making, which can result in patients not being aware of DOACs as a therapeutic option. Most patients on warfarin reported no or limited involvement in decision-making. These patients were not informed about DOACs and had no opportunity to influence the choice of therapy prescribed. As some patients prescribed warfarin would have preferred DOAC therapy, lack of involvement in decision-making was a barrier for DOAC use.

Patient narratives identified that main barriers for patient involvement included some patients viewing it was the clinician's role to make decisions or did not think they could be involved due to historical ways of consulting, patient’s lack of knowledge about AF or oral anticoagulants and thus confidence in making-decisions, not seeing a regular clinician and lack of relationship, acute hospital admission, and limited time in consultations. Lack of therapy options presented resulted in some patients having
negative experiences with warfarin as it did not align with their lifestyle and thus, they experienced challenges with attending required monitoring and taking correct doses.

Several barriers to DOACs use were linked to characteristics of consultations. Firstly, limited consultation time, especially in primary care, was highlighted as a barrier. Interview narratives indicated that there was not enough time to discuss different oral anticoagulant options. Thus, patients perceived that they were informed about an oral anticoagulant preferred by the prescriber. Consequently, prescribing decisions were seen to be influenced by prescriber preferences, which could be a barrier to DOAC use if warfarin was favoured. Some suggested that longer consultations were needed but noted it would not be feasible due to a shortage of clinicians in the healthcare service. Required additional time was also noted to add extra spending in the already perceived cost-conscious healthcare system. Secondly, the timing of the initial consultation was important. Some patients discussed that in situations when they were unwell and concerned with surviving or getting better, e.g. acute hospital admission, they were not able to take in the information and be part of the decision. Thus, the prescribed therapy was based on prescribers’ preference. Thirdly, some patients argued that patients already established on warfarin would not be informed about DOACs due to additional clinicians’ time required and the high cost of DOACs.

Participants also showed knowledge about the higher cost of DOACs compared to warfarin, which was highlighted as a potential barrier to their use in the "cash-strapped NHS". Although some patients viewed DOACs as less expensive than warfarin due to frequent monitoring needed for warfarin in the long-term, some patients were of opinion that warfarin was favoured by prescribers due to cost. They believed it was one of the reasons why they were not told about DOACs.

Patients describing making decision with a clinician or by themselves were told about more than one therapy option. They had an opportunity to voice their preferences, which were shaped by their knowledge about oral anticoagulants gained from their clinicians or social network, perceived safety of oral anticoagulants, and how well it would fit with their lifestyle and work arrangements. Familiarity with warfarin facilitated the choice of warfarin for some patients, whereas the unknown side and long-term effects, and lack of monitoring with DOACs raised safety concerns for others. Some patients who knew people experiencing side effects with warfarin and the inconvenience of taking it tended to choose DOAC therapy. These patients valued the
lesser interference of the medicine with their daily lives more than frequent monitoring which was perceived to be a safety net by some patients. Also, knowledge about DOACs motivated some patients having challenges with warfarin therapy to enquire with clinicians about switching. Thus, lack of knowledge about DOACs and safety concerns acted as barriers to DOACs use.

5.5 Strengths and limitations

The findings and transferability of findings to different settings and patient groups should be considered in the context of the study strengths and limitations. The main strength of this study was a moderate sample size and recruitment of patients from three health economies with different anticoagulation service provision models (see Chapter 4). Also, semi-structured in-depth interviews provided rich and varied lived experiences, enabling greater insight into potential barriers for DOACs use. Lastly, data analysis robustness was ensured by more than one researcher being involved in the process and development of themes and subthemes (see Chapter 4).

It is noted that the sample comprised almost exclusively of White British participants and this is not fully representative of the wider population of the UK. The study also relied on participants’ accounts of consultations when oral anticoagulant therapy was initiated, which could be affected by recall bias. Lastly, participant validation, which could have increased the internal validity of results, was not undertaken. Instead, discussions with PPI advisory group were carried out to ensure data represented patients’ experiences (see Chapter 4).

This chapter has explored the perspectives of patients on factors affecting the uptake of DOACs. The next chapter will present findings from interviews with healthcare professionals and key stakeholders.
Chapter 6 Factors affecting the uptake of new medicines: perspectives of healthcare professionals and key stakeholders

6.1 Introduction

The systematic review described in Chapter 2 identified a broad range of factors affecting the uptake of new medicines within healthcare organisations. However, the review also highlighted that studies reporting factors affecting new medicine use lacked exploration of the wider prescriber (e.g. motivation, values and goals, or beliefs about new medicines) and organisational (e.g. readiness for innovation, culture and climate, implementation process) factors reported in the implementation literature affecting the implementation of health innovations. Deficiency in reporting these factors could be due to the data sources used by the reviewed studies (mostly secondary administrative data from various databases) and lack of theoretical frameworks used to inform study designs of the reviewed studies. Also, in the reviewed studies, the cost of innovation was considered in the context of patient socioeconomic status and reimbursement conditions without discussion of wider health economic costs. Furthermore, the majority of studies were conducted in the USA and identified factors might not be applicable outside the US healthcare system. Therefore, a qualitative study was undertaken to explore perceptions of healthcare professionals and identified key stakeholders involved in the implementation of DOACs on the factors affecting the uptake of DOACs.

The methods used to recruit health professionals and key stakeholders and analyse the collected data are described in detail in Chapter 4. In summary, healthcare professionals involved in the care of patients with AF and key stakeholders involved in the implementation of new medicines within the studied health economies were recruited from primary and secondary care. Also, key stakeholders from relevant national organisations were recruited. Participants were interviewed using a semi-structured interview guide. The interviews were undertaken between March 2019 and October 2019. The following sections of the chapter present characteristics of the interviewed participants, findings from the data analysis, a summary of the findings, and strengths and limitations.
6.2 Sample characteristics

Forty-six healthcare professionals and identified key stakeholders were interviewed in the study. The participant characteristics are summarised in Table 6.1. The semi-structured interviews were face-to-face and lasted between 20 and 63 minutes (average 38 minutes).

6.3 Framework analysis results

Interviewed healthcare professionals and identified key stakeholders recalled the process and their experiences of DOACs being introduced in their practice, organisation, and the studied health economies. Participants discussed how the anticoagulation practice and services changed with the introduction of alternatives to warfarin and reflected on the barriers and facilitators they experienced to DOAC use. Four themes were identified during the analysis (Figure 6.1). Each theme contained three to four sub-themes. Distribution of identified sub-themes in each participant’s transcript is presented in Table 6.2. The themes and sub-themes are discussed in detail in the following sections and supported by representative quotes from participants.
Table 6.1 Characteristics of interviewed healthcare professionals and key stakeholders.

<table>
<thead>
<tr>
<th>Participant name*</th>
<th>Health economy</th>
<th>Patient-facing role</th>
<th>Place of work, role</th>
<th>Setting</th>
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<td>P1-A-N</td>
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<td>Yes</td>
<td>General practice, specialist nurse</td>
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*Participant name included participant number (e.g. P1), health economy the participant was from (A, B, or C), role of the participant (N - nurse, P - pharmacist, GP - general practitioner, C - consultant, O - other, PI - pharmaceutical industry representative).*
Figure 6.1 Summary of developed themes and subthemes from the interview data with healthcare professionals and key stakeholders.
Table 6.2 Distribution of developed sub-themes in each participant’s transcript.

<table>
<thead>
<tr>
<th>Patient-facing role</th>
<th>Value of Innovation</th>
<th>Sociological influences on clinician prescribing</th>
<th>Local health economy readiness for change</th>
<th>External health system context</th>
<th>Commercial influences</th>
<th>Total identified sub-themes (n)</th>
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<td>Real-world effectiveness</td>
<td>Safety profile</td>
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<td>Practical convenience</td>
<td>Clinician capability</td>
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6.3.1 Value of innovation

Interviews revealed that the value of innovation, i.e., DOACs, was considered and discussed by both clinicians and decision-makers. DOACs were compared to the established warfarin therapy to demonstrate and justify their value or lack of it. Perception of their value, low or high, influenced prescribers' willingness to use DOACs in their practice and commissioners' decisions on policies within local health economies. The theme is presented in four sub-themes: real-world effectiveness, safety profile, affordability, and practical convenience.

6.3.1.1 Real-world effectiveness

This sub-theme presents participants' views on the efficacy of DOACs and warfarin and how it influenced the use of DOACs. Many participants discussed if the efficacy of DOACs demonstrated in clinical trials translated into routine clinical practice, and the level of uncertainty varied between clinicians. Some participants viewed DOACs to be as effective as warfarin and better than inadequately controlled warfarin therapy. DOACs were perceived to offer immediate risk reduction of AF-related stroke, whereas warfarin took at least a couple of days. Hence, these clinicians favoured DOACs over warfarin.

“They [DOACs] have been tried and tested in several randomised clinical trials with data showing equivalence to warfarin, and some trials showing that they were actually in some cases better than warfarin. So, why with a drug which you can just say to a patient here is a tablet, take it, and they are protected immediately, would you deny a patient.” (P18-B-C)
Some also described DOACs as more stable and reliable than warfarin due to less food or drug interactions and less significant effect of patient's health changes on DOACs' effectiveness. These clinicians commented DOACs would be more effective than warfarin in patients with frequent hospital admissions, multiple comorbidities, and taking medicines that interact with warfarin.

“The DOACs are far more reliable. You know, you are not getting the swings that some of the patients get with warfarin.” (P20-B-P)

Some viewed DOACs to be very similar to each other, potential differences in effectiveness were not significant, thus not influencing their prescribing decisions. Others noted efficacy could be different between different DOACs for patients with certain clinical characteristics. Thus, choosing between different DOACs, when no clinical trials had compared all DOACs directly, was sometimes challenging. For instance, some commented that dabigatran was “out of favour” as there were concerns with increased risk of myocardial infarction.

“The difficulty I suppose with the DOACs is there is no direct comparison between them. There is no trial for all of them together. They are always the agent versus warfarin.” (P32-C-N)

Others had the opinion that there was limited real-world data to assure the efficacy demonstrated in clinical trials. Some noted a lack of evidence in certain patient groups such as patients with low or high body weights. Others were concerned with the patient's adherence to DOAC therapy in practice as the adherence in clinical trials was perceived to be better than in real-life practice. Some believed that the impact of non-adherence to therapy had more impact to reduce the efficacy of DOACs than warfarin. They argued that DOACs had shorter half-lives than warfarin. Also, DOACs had no frequent monitoring like warfarin, which might lessen the significance of taking them and adherence could not be assessed or monitored. Thus, some perceived well-controlled warfarin therapy to be superior to DOACs. Hence, these participants preferred warfarin over DOACs.

“People in trials generally do better than people who aren’t in trials, yes, in terms of compliance etcetera … I think people who are able to take warfarin, who have got good compliance, will probably get better outcomes in a real-world situation than people on these newer agents.” (P39-C-C)
Compliance was of particular concern for clinicians when patients, with poor adherence, had been switched to warfarin because of inadequately managed warfarin control. In their view, these patients would be non-adherent to DOAC therapy as well. They argued that frequent monitoring of warfarin could encourage adherence as clinicians could assess adherence more regularly and motivate patients to take warfarin. In comparison, DOACs had no monitoring and, thus, no opportunities for clinicians to support adherence to the therapy.

“They [patients] won’t take DOACs in the same way as they don’t take the warfarin. And in some cases, they take warfarin better because they come in every month and somebody is giving them a bit of ‘now have you been taking them?’ and if you've got a good relationship with your patients, they would give you honesty and be able to tell you whether they're taking it or not.” (P14-A-P)

Some clinicians admitted that they preferred once-daily dosing DOACs rather than twice-daily to promote adherence. Some also noted that some patients were non-adherent to warfarin due to misunderstanding the prescribed dose as it often changed, whereas the dose of DOAC remained the same. Other clinicians argued that many medicines, including medicines reducing the risk of stroke, e.g. antihypertensives, were not regularly monitored to ensure adherence or that they were working. In their view, instead of refusing to use DOACs due to concerns of adherence, clinicians should educate patients on the importance of taking them and allow patients to be in control of their adherence.

“I tell the patient this is why you’re having it, the risk/benefit, and that you need to adhere to therapy. Now, this is not a school, we are not dealing with children, you know, this is not a prison where you have got to force something down, ultimately then it is the patient's decision on whether they're going to be compliant or not.” (P18-B-C)

Some clinicians observed incorrect doses of DOACs being prescribed, e.g. lower doses than recommended, thus reducing therapy efficacy and increasing the risk of AF-related stroke. They perceived that some clinicians were afraid to prescribe a full dose of DOAC for patients with a risk of falls or bleeds. Also, the lack of knowledge and understanding of different recommended dosing, especially for apixaban, was highlighted as another factor contributing to the issue.
“Audits looking at patients discharged on apixaban is [found] very high low-dose usage and inappropriate dosing … If we find apixaban mis-dosed on discharge, we stop it and change it to another Xa inhibitor [rivaroxaban, edoxaban].” (P2-A-GP)

Finally, several participants highlighted that DOAC therapy was not effective for every patient with AF. Warfarin was perceived to be more effective than DOACs in patients with poor renal function, valvular AF, or mechanical valves.

6.3.1.2 Safety profile

This sub-theme describes participants’ view on the safety of DOACs and warfarin and how it influenced the use of DOACs. Some participants had no concerns about the safety of DOACs as they were licensed in AF and recommended by NICE. Nevertheless, some observed general anxiety about the use of new medicines in the healthcare community. It was due to a lack of real-world evidence confirming their safety and past cases of new medicines being withdrawn in the post-marketing stage due to safety risks. As such, some clinicians described a cautious approach to the use of DOACs till safety was assured in clinical practice.

“Most people can recall some new drugs which were fantastic and suddenly had to be withdrawn from the market because some problem was found with it, so there was a caution.” (P3-A-GP)

Some primary care clinicians were reluctant to start anticoagulation as they perceived it required specialist input due to a historical view of anticoagulants being “high-risk” medicines. Others added that such a view was unintentionally further reinforced by formulary conditions when DOACs were initially restricted to secondary care initiation in health economy B.

“GPs were extremely reluctant. Very nervous about it I would say. [They] did not know much about anticoagulation […] They [GPs] wanted somewhere to refer patients…It was very clear at that time that my colleagues in primary care regarded decision making for anticoagulation as a secondary care issue.” (P15-B-C)

Several clinicians also expressed the frustration of some clinicians not starting anticoagulation due to the perceived risk of bleeding. They commented that there was insufficient understanding of how to use HAS-BLED (bleeding risk scoring tool) recommended by NICE (Lip et al. 2011, Pisters et al. 2010). Thus, it was used inappropriately in the decisions not to anticoagulate patients (whereas it is a tool to
minimise bleed risk and not to decide whether anticoagulant treatment should be offered). In their opinion, patients were not informed of the implications of not initiating anticoagulation therapy, i.e., the consequences of experiencing a stroke.

“*I think [it] is being inappropriately used is the HAS-BLED score, I think that has been used as an excuse not to anticoagulate, which is never what it was meant to do … HAS-BLED score is high, I’d better not give you anticoagulation, so I think a lot of it is unmet need in patients who are recognised to have AF but haven’t been anticoagulated for fear of consequences.*” (P15-B-C)

When discussing the safety of DOAC therapy, most participants commented on the unknown risk of bleeding and a lack of reversal agents. Some healthcare professionals were also concerned that patients' renal function was not considered when initiating DOAC therapy, thus higher than recommended doses were used increasing the risk of bleeding. The message of lack of reversal agents from stakeholders and clinicians raised concerns for some prescribers, particularly for clinicians with limited experience in managing bleeds. Consequently, some clinicians were reluctant to use DOACs.

“The lack of reversal agent was a significant concern to primary care; it was a significant concern to patients with the initial discussions while we became more comfortable. It was certainly a reason that we were cautious about the introduction.” (P15-B-C)

Others commented that protocols for reversing DOACs were developed and included agents that would be used for warfarin reversal also. Some also compared DOACs to aspirin or low molecular weight heparins, which had a similar bleeding risk and no reversal agent, but prescribers were not reluctant to use them. Others, who had experience in managing bleeds or received education about DOACs, argued that DOACs had short half-lives, therefore the reversal agent would be of no use by the time the patient was admitted.

“It [lack of reversal agent] was always a lie because it didn’t seem to affect their [DOACs] safety, the fact that we couldn’t reverse. They are relatively short half-life drugs. If you go into hospital bleeding on a DOAC, by the time they have managed to sort themselves out to get you to the theatre, the anticoagulation effect is going to be wearing off.” (P2-A-GP)
Some reflected that once the reversal agents became available, there was very little demand for them and concerns regarding bleed risk diminished over the years with clinicians becoming more comfortable with DOACs. Some also stated the real-world data did not show an increase in bleeding rates with DOACs as was initially feared. As such, some participants concluded the message of the lack of reversal agent was overplayed and used as a tool to control and limit the introduction of DOACs due to other reasons.

“The lack of reversal agent hasn't been as big an issue as was initially feared, but at the time it was a substantial concern, yeah. It was certainly used as a reason not to introduce them, and I think it was used as a smokescreen to avoid some of the cost discussions that were going on at the time.” (P15-B-C)

Some clinicians had some concerned patients coming back with newspaper articles stating that DOACs would make them bleed, but after receiving an explanation, they were happy to continue with them. Others described how the presentation of information about DOACs reversibility to patients influenced patients’ preferences. For instance, a few clinicians described some patients who refused DOAC therapy after learning, in conversation with their GP, that there was no way to reverse it. However, after receiving more detailed information on how the bleed would be managed, those patients were happy to start a DOAC.

“I know some patients came to the anticoagulation clinic having had a conversation with the GP and being put off DOACs because of the lack of reversal agent, and then I would have a conversation with the patient and go through all the pros and cons and by the end of it, they are like, ‘Oh, no, actually I'd rather have rivaroxaban. Thank you.” (P36-C-P)

Although some participants were concerned with the unknown long-term effects and observed gastrointestinal (especially with dabigatran) or skin-related side effects with DOAC therapy, most participants experienced DOACs being well-tolerated by patients. Some clinicians highlighted DOACs did not cause alopecia or diarrhoea, which occurred in some of their patients taking warfarin. In contrast, other clinicians perceived warfarin as having fewer side effects than DOACs.

“We have had a percentage of patients who have had massively difficult side effects [with DOACs] that they have been unable to continue with, which from warfarin point
of view, apart from the bleeding risk, patients do not really get side effects in the same way as they do with other drugs.” (P10-A-P)

Another aspect of safety many participants discussed was the monitoring of oral anticoagulant therapy. Some participants commented that both clinicians and patients taking warfarin were used to warfarin monitoring and thus viewed that monitoring was needed for DOACs to ensure their safe use, which acted as a barrier for DOACs use. Others argued that many medicines, including other anticoagulants and antiplatelets, were not regularly monitored like warfarin to confirm their ongoing safety.

“They [doctors] are very fixated on the idea of an INR check to make them safe. And yet, in other drugs, we don’t do beta-blocker levels, we don’t do aspirin to look at aspirin levels or something to see whether or not other drugs are working.” (P33-C-C)

Some commented DOACs needed monitoring, for example through tests to check the full blood count, renal, and liver functions. However, there was uncertainty with what to monitor and how frequently as advice differed amongst experts. A few clinicians were concerned that patients on DOACs would get lost in the system as clinicians were not sure of the required monitoring.

“We [GPs] don’t know what monitoring [was] needed, we’re worried these patients are going to get lost in the system. So, there was a lot of anxiety there.” (P1-A-N)

Others did not share those concerns. In their view, patients with AF often had other comorbidities or medicines requiring annual reviews and thus, DOAC therapy would be monitored at least annually. Some clinicians described that protocols and practices were developed to ensure adequate DOAC therapy monitoring.

“We [GP practice team] are hoping in the next few months to create a database of all patients on DOACs and trying to make sure that their monitoring is up to date.” (P6-A-N)

6.3.1.3 Affordability

This subtheme is concerned with the perceived affordability of DOACs within local health economies and what impact it had on the availability and use of DOACs. Most of the participants commented on costs associated with DOAC and warfarin therapies.
Various costs (medicine, monitoring, direct health effects, and opportunity) were highlighted and influenced, to a varied extent, by the decision-makers and clinicians. There was a consensus amongst participants that DOAC tablets were more expensive than warfarin. Some commissioners, e.g. health economy C, accepted the cost pressure from DOACs and described trying to make savings in the medicines budget through other means. Some participants noted commissioners in some health economies were concerned about managing local medicine budgets and if they could afford to fund high use of DOACs. The number of patients who could benefit from them was increasing at the time due to local and national initiatives to identified undiagnosed patients with AF. Subsequently, some participants commented that some health economies initially chose a controlled entry of DOACs to manage limited medicines budgets. Warfarin was a cheaper and effective medicine, thus was advocated as a first-line oral anticoagulation therapy. Some participants critiqued this approach due to a lack of consideration of cost-benefits associated with DOAC therapy, lack of a patient-centred approach, and prioritising managing costs over patient safety.

“They were concerned about the cost of the DOACs … they didn't want it to be open for everybody. They were worried about that. They wanted to keep warfarin as first-line.” (P15-B-C)

“If it [DOACs] had been the same price as warfarin people would have just let it happen … I’m still of the belief that actually the main driver for looking at the reasons for managing the entry of these drugs was around cost. Only once cost was considered was then a process put in place in order to manage patient safety.” (P25-B-P)

Some noted that associated monitoring with warfarin, e.g. clinicians’ time, operating costs, made DOAC therapy with limited monitoring similarly expensive, or even cheaper for patients requiring very frequent warfarin monitoring. Others, despite the monitoring costs associated with warfarin, regarded it as a cheaper therapy. Some participants involved in commissioning and management of new medicine entry stated that the warfarin monitoring service cost varied between different health economies. There was no national tariff for the service. The warfarin monitoring service in health economy A was regarded as expensive despite a recent review and cost reduction, thus making DOACs as expensive or even less expensive than warfarin therapy. In
health economy B, the service was described as a relatively low cost. Thus, warfarin therapy with associated monitoring was perceived to be less expensive than DOAC therapy.

“The costs of that [warfarin monitoring service] varied wildly between PCT [before CCGs] to PCT to PCT, and some of it was secondary care led models, some of it was primary care led models, some of it was a mix of models, some of it no-one bloody knew what the cost was.” (P12-A-O)

In health economy A, providers were paid per patient appointment, thus reducing the number of new warfarin patients resulted in savings for the health economy. In health economy B, a service package fee was agreed between commissioner and provider, and it was not influenced by increasing or reducing the number of patients. Thus, some commissioners discussed that theoretical savings from reduced warfarin monitoring as more patients would start DOACs did not translate into reality. They also stated that warfarin service could not be decommissioned as not all patients could or wished to be on DOACs.

“There was a lot of discussion about potential savings in terms of the impact on anticoagulant clinics. It became very rapidly clear that we are not going to be able to close down the anticoagulant clinics; they will still need to be paid for, so those potential theoretical savings were not going to translate into reality.” (P15-B-C)

Some also commented that DOACs were deemed as cost-effective by NICE due to lack of associated monitoring costs. However, they observed that in practice some clinicians were performing extra monitoring, e.g. anticoagulation activity, or were paid for initiation by commissioners, reducing the cost-effectiveness of DOACs. In their opinion, the additional monitoring costs of DOACs in real practice were not considered in commissioning decisions or decisions were not reviewed.

“It's [DOAC] a more expensive drug, but you don't need to do the monitoring. Therefore, you don't have the monitoring costs. The health economic models took that into account. Subsequent to NICE, there were recommendations about bi-annual renal monitoring … so, a subsequence of NICE we know that there's a lot of INR monitoring that goes on … but that would make the cost exceed the NICE threshold. But no one cares about that stuff; NICE has said yes.” (P12-A-O)
Others also considered direct health effects costs, such as prevention of stroke and management of bleeds, when making decisions. Some commented that existing reversal agents or other therapies for managing significant bleeds due to DOACs were much more expensive than vitamin K used for warfarin. Thus, they were cautious with the use of DOACs.

“You can do platelet transfusion that was something blooming expensive to do, so they [clinicians] did not particularly want to go down the avenue of doing infusions”.

(P11-A-P)

Others commented that stroke was more expensive due to associated health and social care costs than DOAC therapy. Thus, some thought that use of DOACs despite their high cost was justified, especially in patients with increased risk of stroke, e.g. inadequate warfarin control, refusing, or reacting to warfarin.

“When you look at the cost of a stroke for the NHS and social care, you know you’ve got your hospital admission, you’ve got rehab, you’ve got social care, you’ve got people needing nursing homes, etc, so I think, I seem to remember circulating that data made people realise that it was worth it. You know you’ve got to look wider than just our drug budget.” (P36-C-P)

A couple of participants also discussed the opportunity costs. They argued that the same clinical outcomes could be achieved with well-controlled and more cost-effective warfarin therapy. In their view, additional money spent on DOACs with no added clinical benefit would lead to less funding available for other healthcare and social care services, e.g. mental health, that could bring greater social benefits. Consequently, they thought that the use of DOACs would cause detriment to the local population and thus favoured warfarin.

“Being brutally blunt, the NHS at that time could not and certainly cannot now afford what it’s spending its money on. It's not cost-effective. The opportunity cost is shit care for your gran, less investment in mental health services, less investment in social care, less investment in therapy services. And no one really thinks about that stuff.” (P12-A-O)

When discussing local health economy medicine budgets, some commissioners revealed payments for medicines and their monitoring were made from separate
budgets. When making commissioning decisions, only the medicines budget and not the monitoring costs were considered. Thus, the true cost of therapy at the time of decision-making was unavailable and not always considered. Hence, warfarin with lower acquisition costs was preferred.

“They [medicine and monitoring costs] don’t come out of the same budget. They come out of the same overall budget, but nobody looks at how much warfarin costs in my drug budget, that is not linked together … the CCG will pay for them both, but they’re never looked at together. So, we’re really bad at that in medicines. We know about it, but we don’t necessarily take that into account.” (P9-A-P)

Additionally, some noted that the savings from using DOAC therapy, e.g. stroke prevention, reduced clinic times, was difficult to demonstrate to local decision-makers. Those savings could take a couple of years to be realised and went into budgets other than the budget that funded DOACs. Thus, some commissioners in health economy C used information from economical models to inform their decision-making. Local models supported the certain ratio of DOACs to warfarin use by showing financial savings in terms of reduced incident stroke within the first year and over the remaining lifetime of patients.

“A health economist … did some modelling for NHS England on the economic footprints of anticoagulation … I was able to substitute [to] … actual local costs for warfarin and for DOACs … then I could remodel it on a where the break-even point would be in terms of the warfarin/DOAC ratio.” (P42-C-O)

Several clinicians said the cost of DOACs did not influence their prescribing decisions because NICE recommended them. Some commissioners commented that it was unlikely for clinicians to consider therapy costs as they were not aware of them, did not manage medicine budgets, and therapy-associated costs did not come off their service budget. Some also suggested GP practices without warfarin monitoring services would be inclined to send their patients to a secondary care clinic as it would bring savings for the practice, e.g. clinician's time. Thus, some highlighted that overall health system costs associated with DOACs were not considered in decision-making, especially by clinicians.

“It works in silos. The cost to a hospital doesn't come into the decision of somebody in GP land looking at their budget. They don't consider the extra. If they could pass
that over to secondary care well, then that means they’ve saved money. So that’s a false balance sheet.” (P45-O)

6.3.1.4 Practical convenience

The consensus across interviewed participants was that DOAC therapy was more convenient than warfarin. Warfarin initiation was perceived as a complex process requiring tasks to ensure desired anticoagulation levels were achieved, in-depth discussion with a patient on therapy practicalities, and organisation of future monitoring. Whereas some participants valued how clinicians could initiate DOACs without needing to refer to a specialist anticoagulation service or perform additional monitoring. Thus, it was viewed as an easier process of starting anticoagulation. In their opinion, the use of DOACs led to safer and quicker discharges from secondary care, saved clinician's time in consultations, and GPs could manage their patients themselves.

“As a junior doctor working in a hospital to initiate warfarin it is really difficult because you have to get them loaded, you have to explain quite a lot of detail to a patient what warfarin is, what's good and what's bad about it. You then, and this is the crucial bit, you have to arrange ongoing warfarin monitoring, and you haven't a clue whether that patient is going to have their warfarin tested in clinic X or by GP Y or by domiciliary phlebotomy services … and it takes time, and they are very likely to get it wrong. A DOAC is dead easy, you just fill in TTO [discharge letter], and it's done.” (P3-A-GP)

Many clinicians took anticoagulation therapy convenience for the patient into account when suggesting therapy options to patients. Some clinicians highlighted that DOACs had simpler dosing regimen with no or limited dose changes, whereas changes in warfarin dosing were frequent. Some clinicians viewed DOACs of particular benefit for patients with memory impairment, e.g. patients with mild dementia.

“I think especially around dementia and the likes that are easier to keep control of than warfarin, so whenever possible, we do encourage DOACs for patients – especially MDS [mild dementia symptoms] because if the patient hasn’t got capacity to remember warfarin doses and let’s face it, more often than not the way dose gets changed, there is a chain that is very difficult to follow.” (P20-B-P)
Some also added that the choice between DOACs was influenced by the ease of prescribing and taking it. For instance, some GPs commented that apixaban dosing was confusing, and it required adjustments for increasing age, thus was used less. They also noted that DOACs, except dabigatran, could be put in patient's compliance aid to help with adherence.

“We [in GP practice] tend to use rivaroxaban or edoxaban. Partly because of the once daily regime, which is easier for a lot of patients and the fact that they can go in dossette boxes. Apixaban I probably use less. It is the dosing we do find quite confusing and got [to] really think about it and sometimes it is just easier to use the other once daily preparations.” (P1-A-N)

Other clinicians commented on warfarin having an onerous impact on patients’ daily life. In their opinion, associated monitoring with warfarin caused difficulties for patients who were in employment, home-bound, or without their own transport. Some clinicians reported some patients refused warfarin or wanted to switch due to the inconvenience of monitoring. Also, DOACs had fewer interactions with food and alcohol, needing fewer changes to patients' diet. Thus, some clinicians preferred DOACs over warfarin.

“The faff about having to normalise or getting the INR within target and the interactions that warfarin has with other drugs and food and everything else, overseas travel, convenience for the patient, just convenience really. It frees the patient up to do other things.” (P7-A-GP)

6.3.2 Sociological influences on clinician prescribing

This theme presents sociological influences on clinician decision-making when prescribing oral anticoagulants. Identified sociological factors included patient clinical characteristics, clinician capability, peers influence, and clinician-patient interaction. The theme is presented in three sub-themes: clinician capability, peer-network influence, and patient factors.

6.3.2.1 Clinician capability

This sub-theme discusses the perceived ability of clinicians to use oral anticoagulants in clinical practice and availability (or lack) of resources, enabling them to do so. Knowledge about anticoagulation, including DOACs, varied between clinicians across the studied health economies. Some participants noted that the reluctance to use
DOACs was notable amongst some primary care clinicians, who were previously not involved in warfarin monitoring service. Many participants described some GPs, especially in health economy B, lacking knowledge about the condition and oral anticoagulants and thus confidence in using them. Others commented there was nervousness and fear about DOACs being initiated in primary care amongst some commissioners and GPs. Consequently, those GPs preferred patients requiring anticoagulation to be managed in secondary care and referred them to the provided service. However, many participants viewed that anticoagulation should be managed in primary care. Hence, implementation of DOACs also required changing views of some GPs.

“There is a little bit of deskilling … within primary care, where GPs historically haven’t managed anticoagulation very much at all, they've handed anticoagulation to the secondary care … [some GPs] don’t have the confidence to sometimes get on and treat these patients … and they just hand it off.” (P17-B-N)

“I have given talks to GPs about use of anticoagulants, the pros and cons of different agents and that has been something raised not so much recently but more so in the past by GPs who felt ‘This isn’t my job.” (P33-C-C)

Some argued it was difficult to develop the required skills for initiating anticoagulation because GPs did not see many patients with AF requiring anticoagulation in their practice. Others noted with the increasing use of and familiarity with DOACs some GPs gained experience and knowledge and became confident in using DOACs in their clinical practice. Some reflected there are now more clinicians comfortable prescribing DOACs than five or six years ago.

“Some GP practices decided that actually having gained some experience of prescribing the drugs on the amber drug guideline, that they would be happy to initiate lower-risk patients … not all GP practices took that up, some of them chose not to … there is still a relatively small number of practices doing that [initiating DOACs].” (P21-B-C)

Contrarily, some participants observed that GPs with previous experience of using anticoagulation were more willing to use DOACs for patients with AF. For instance, in the health economy A rivaroxaban was used for deep vein thrombosis treatment as part of a clinical pathway in primary care. Thus, GPs were seen to have gained
experience and confidence in using it. Some commented that it was one of the reasons for the high use of DOACs in health economy A by primary care clinicians.

“If you thought somebody had a DVT and you would probably see about ten a year, you needed to know [how to] use rivaroxaban, and it gave the GPs a confidence in using the drug and all of a sudden we saw it exploding into AF at the same time because the GPs had got used to it in a mandated pathway [the DVT pathway].” (P2-A-GP)

Furthermore, warfarin monitoring services in health economies A and C were provided by primary and secondary care. Thus, GPs involved in the service were perceived to have a good understanding of the condition and anticoagulation, resulting in being more confident and comfortable in managing anticoagulation and using DOACs.

“I think having a knowledge of anticoagulation through running the warfarin service made me feel more comfortable in terms of identifying with the patients who would benefit from it. And a lot of the conversations around warfarin monitoring included conversations about DOAC initiation and monitoring.” (P3-A-GP)

A couple of participants were worried that as the use of DOACs increased, the use of warfarin decreased and with it the knowledge and confidence in prescribing it. Thus, they anticipated the use of DOACs to continue increasing amongst clinicians.

“I see a massive reduction in warfarin, which also has its cons because now people are not as good at using warfarin.” (P31-C-P)

Some discussed that commencing DOACs required relatively long appointments to assess the patient, explain the need for anticoagulation, and discuss different therapy options. In their view, it was challenging to have such conversations in time-constrained with the high workload in primary care where patients presented with multiple health complaints and the standard appointment time is 10 minutes. Hence, some GPs preferred anticoagulation managed in secondary care as they did not have the means to facilitate long enough consultations for informed discussions about anticoagulation with patients.

“The average patient comes in with over three problems, so how are you going to fit anything else into that? You need the whole really ten minutes, so when you’ve got
30 seconds, how do you do that? You can't discuss anticoagulation in 30 seconds, not properly.” (P13-A-P)

“I think in a lot of cases it was you know, we're busy, we've got a lot of things to do, there's a service there that can do that for us, so we'll pass it on to them really.” (P19-B-O)

Others commented that secondary care experienced different pressures and could not see all patients with AF requiring anticoagulation. They argued that the anticoagulation of patients with AF should be undertaken in primary care, but the commissioner must appropriately resource the additional workload required. Some clinicians commented how commissioners in some areas did not recognise that initiating and monitoring DOACs created new work for general practices. Thus, some AF improvement programmes failed to achieve the desired outcomes.

“As soon as you ask primary care to do anything, very rightly they will say to you, where is the resource for this coming from? I am stretched way beyond my means, how am I going to do this? And some CCGs don't really get that and unfortunately, for instance, some of the programmes in atrial fibrillation in other areas … have done very poorly.” (P13-A-P)

Some participants noted that some GPs wanted the initiating and monitoring of DOACs to be a commissioned service like warfarin monitoring service. As some participants commented, commissioners were not willing to pay for the service as it was perceived to be part of the general medical services contract. However, GPs in health economy C were offered a fee per patient initiated on DOAC therapy, but the uptake was low. Some commissioners reflected it was due to a mixture of factors including lack of skills in anticoagulation, lack of capacity within the GP practice, and difficulty to employ additional staff to do the work.

“We actually offered [funding for DOAC initiation] for last year; we offered a payment of £66 to initiate to DOACs. It was quite a poor uptake of that.” (P30-B-P)

6.3.2.2 Peer-network influence

This sub-theme describes peer influence on the use of DOACs and changes to clinicians' prescribing practice. Some participants commented it was difficult to change clinicians' prescribing habits, and it was common to experience resistance to change
in practice. Others noticed that prescribing habits of oral anticoagulants changed slowly.

“A lot of prescribing is habitual, so basically clinicians will then prescribe bucket loads of it before the newer medication gets a foothold in the door. And then it is harder to kind of get those habits changed.” (P44-PI)

Some clinicians commented that they could consult with more experienced clinicians in their direct or indirect teams. The available support facilitated the use of DOACs in more complex patients.

“When I first started, I guess I had a team of people around me that were more familiar using DOACs, so I had them to consult when I first started prescribing DOACs.” (P8-A-N)

Others commented they started using DOACs when they saw them being prescribed in practice. Some primary care clinicians noted that seeing secondary care colleagues using DOACs encouraged them to use DOACs for their own patients. Some clinicians in primary and secondary care also stated that they used a certain DOAC because they noticed it being favoured by their peers in secondary care. Others commented that secondary care clinicians were (at least initially) driving the use of DOACs, especially in health economy B. Endorsement of DOACs by secondary care colleagues increased confidence in these medicines for some GPs. Some even confessed they now rarely discuss or offer warfarin to patients in consultations. Also, others identified that patients should have the same therapy available despite the setting, thus started using DOACs in their practice.

“Probably the growing numbers of patients initiated on DOACs in secondary care. And most of us would realise this is crazy; you can’t have a patient receiving treatment at the hospital, which is completely different from the treatment they would receive at primary care.” (P3-A-GP)

Most primary care colleagues also identified their peers in primary care (within the same GP practice or health economy) influencing their prescribing habits. In health economy A, many participants identified that primary care was driving the use of DOACs as it had locally and nationally recognised GPs with specialist interest (GPSI) in AF and cardiovascular disease, who promoted the use of DOACs. Local champions
were perceived to have a huge influence on primary care clinicians prescribing behaviour. Support from secondary care clinicians was also noted as important despite some participants stating that primary care was leading the implementation of DOACs.

“*I think having a strong GPSI [General Practitioner with a Special Interest] base here [health economy A] and the confidence to prescribe it has influenced the other GPs as well.*” (P7-A-GP)

“I would say primary care was the main driver. The haematology team were on board, so they were interested, but there were reservations … it was being driven very heavily by the prescribing lead GP, [who] was very heavily involved in pushing this particular project.” (P10-A-P)

In contrast, in health economy B, no primary care champion was identified by the participants. Instead, secondary care formed opinions and lead to the implementation of DOACs prescribing. The opinions differed between secondary care with some clinicians pushing for greater use of DOACs and others opposed to their widespread use. Several participants commented that discussions about DOAC use were dominated by one clinician who was perceived to be very cautious about DOACs, which potentially led to slower uptake of DOACs within the organisation and delayed spread to primary care.

“I think we have got a very cautious haematology department here and they’re always extremely cautious about change, and this then reflects. If there is a drug that is an anticoagulant, it usually goes through them when they’re in the various committees, and they’re the ones who kind of put up certain barriers and slow things down.” (P16-B-P)

Several clinicians noted that they used the DOAC, which was used the most in the local community to ensure safe prescribing. Others highlighted that the preference for DOAC within local communities was changing over time. For instance, the use of apixaban and edoxaban was increasing. Some also noted differences in preferred DOAC agents between primary and secondary clinicians. Primary care tended to favour rivaroxaban, whereas secondary care leaned more towards apixaban. Others stated that peers’ prescribing habits did not influence their choice of DOAC.
“I should choose the one that me and the health community I live in use the most because that way we hopefully can avoid mistakes.” (P2-A-GP)

“I think hospital clinicians are more likely to choose apixaban, I think a GP in primary care is more likely to go for rivaroxaban – that’s my observation.” (P36-C-P)

### 6.3.2.3 Patient factors

Interviews revealed that patient factors influencing prescribing decisions were patient clinical characteristics and therapy preferences. Some clinicians stated they did not have a preferred oral anticoagulant. Instead, they prescribed therapy that was the best suited for the patient. Other clinicians described stating their preference for therapy but still made the patient aware of alternative therapy options.

“I have not got a particular one that I prefer or do not prefer. It is very much trying to tailor it to the patient really.” (P32-C-N)

“Depending on the patients’ characteristics I will normally select one for them, give them my preferred agent for their particular situation and then if they say “Oh have I got to take this drug twice a day have I? Not once, like warfarin? Oh I can’t cope.” Then I might say “Well you can take rivaroxaban but that might interact with some of your other drugs more than apixaban might or your renal function is not so good. So that’s the way I would do it and talk about the risks and benefits.” (P33-C-C)

Clinical characteristics that clinicians mentioned included the patient's renal and liver functions, other prescribed medicines, comorbidities, and degree of frailty.

“It also comes down to the frailty of the patient. Do they eat regular meals? What is their renal function like? Yes, I would go on to assess according to that, but I will always say there are four different types, and there's warfarin as well.” (P8-A-N)

Most clinicians also revealed that patients with well-controlled warfarin therapy were not usually informed about DOACs unless they struggled to attend monitoring appointments. Additionally, warfarin's inadequate control triggered some clinicians to suggest to patients established on warfarin switching to DOAC therapy.

“I would only talk about DOACs if I looked at a patients’ time in therapeutic range and I thought it was below 60% or like you know it was very low, and I could not see any change happening in bringing it up.” (P5-A-P)
A few clinicians described presenting patients with one therapy option, their preferred DOAC. They argued that there were insignificant differences between different DOACs (excluding dabigatran) to spend the limited consultation time discussing all available DOACs. Participants also described how in other conditions, like hypertension, patients are not presented with different antihypertensive options. Instead, the clinician decided on the agent to prescribe to achieve the desired clinical outcome.

“We offer them anticoagulation. If you were to come to me with your hypertension, I wouldn’t offer you different ACE inhibitors or ARBs or calcium channel blockers. The Xa inhibitors are the Xa inhibitors, and I don’t believe there is sufficient in the evidence to justify different choices.” (P2-A-GP)

In contrast, many clinicians described attempts to involve new patients diagnosed with AF in decision-making. However, some commented that some patients, more often older patients, did not have any questions, wanted to be told what to do, and trusted the clinician to decide. When presented with therapy options, these patients passed the decision-making responsibility to the clinician. Subsequently, patients who declined or were not given the opportunity to be involved in the decision-making did not influence the prescribing decision.

“I would say some patients want limited involvement in decision making. Some patients are quite happy to hand off responsibility because they don’t feel that they can take on board the information we’re giving them and make an informed choice. So, it’s very common that patients will say if you were me, what would you do, or if I was your mum or if I was your dad, what would you be telling me to do.” (P17-B-N)

As stated by many clinicians, some patients wanted to learn about different therapy options and voice their therapy preferences. When patients presented with options and explained advantages and disadvantages, some clinicians noticed they, especially younger patients, were increasingly choosing DOACs over warfarin. Some of these patients were aware of warfarin through their social network (e.g. family, friends). They had formed a negative view of warfarin due to its monitoring burden, and its association with rat poison. Hence, they preferred DOAC therapy. Some patients also learned about a positive experience with DOACs from their social network and chose DOAC therapy. When choosing between DOACs, some patients based the decision on it being a once or twice daily medicine. Simultaneously, some
clinicians noted that positive experience with warfarin or negative experience with DOACs (e.g. experiencing a side effect) in patients' social circle influenced some patients to choose warfarin.

“Patients who have had family members or friends who have had the DOACs and certainly younger patients and mobile patients who didn't want to be tested all the time, we had a lot of that ... you get the odd patient who's got a family member who's had warfarin, or they've had some friend, or they've had some side effects or problems with the DOAC who would want warfarin, but they tend to be older patients.” (P7-A-GP)

Furthermore, some clinicians experienced some patients who were currently taking warfarin enquiring about DOACs during their warfarin monitoring visits. These patients found out about DOACs from their social network, internet search, popular press, or the AF Association website. After receiving more information from the clinician, some patients were switched to DOAC therapy, and some wanted to continue warfarin. Some even admitted that patient demand for DOACs encouraged clinicians to use more DOACs in their practice.

“They [patients] would read, they would google, they would hear neighbours saying: ‘Oh I used to be on warfarin, but I'm no longer, I'm on this.’ Yes, they do come and ask. And then when they ask if they are all right, we fast forward that request to the doctor.” (P4-A-P)

Some participants noted that the patient's choice was also influenced by how they presented information about DOACs and warfarin. Some perceived that DOACs were presented positively with downplayed bleeding risk and lack of reversal agent compared to warfarin. Thus, DOAC therapy was shown as a more convenient medicine for the patient.

“I think when you try to explain it to patients: ‘Okay, I can start you on this medication, and it will start working within two days, and we'll see you in a year.’ And then you compare that with an ‘Okay, we'll start this medication slowly, you have to attend the nurse and INR, and then you have to check it a few days later, and keep doing that, come back regularly for several weeks.' I don't see how you could construe that as more convenient to the patient.” (P37-C-GP)
6.3.3 Local health economy readiness for change

The theme examines the willingness of decision-makers and the capability within local health economies to implement DOACs. The theme is presented in four subthemes: innovation-health economy fit, collaborative work, activities supporting innovation, and promoted prescribing practice.

6.3.3.1 Innovation-health economy fit

This sub-theme explores how the innovation aligned with the existing goals, priorities, and ways of working of the local health economy and resulting influence on the openness to the use of DOACs. Many participants across all three studied health economies stated reducing the risk of AF-related stroke received much attention from both commissioners and clinicians coinciding with the introduction of DOACs. Some commented it was due to a combination of observed low local anticoagulation rates, changes to national directives (e.g. NICE) and policies (e.g. the General Practice Quality Outcomes Framework), and national campaigns to identify undiagnosed patients with AF. Hence, increasing local anticoagulation rates in AF was on a priority list for many clinicians and commissioners, resulting in the delivery of various local initiatives.

“There was a time 50-odd % of the AF population receiving anticoagulation. It was good quality anticoagulation, but there’s only 50% when it should have been about 85%. So, we pushed really hard on that for a year-and-a-half using a whole bunch of very methodologically applied quality improvement techniques of various types and flavours.” (P12-A-O)

As some noted, the collective aim of those initiatives was to increase anticoagulation rates and consequently reduce the incidence of AF-related strokes. Some also added that promoting the message of preventing strokes rather than just achieving anticoagulation rate targets engaged more people with the local initiatives, including the use of DOACs. Thus, many participants viewed and promoted that the choice of anticoagulation therapy, warfarin or DOAC, was of little importance. Also, a few participants reflected that the achieved improved anticoagulation rates would have unlikely been achieved if warfarin was the only therapy option.

“Our focus was really on getting patients on an anticoagulant rather than specifically worrying about whether it was warfarin or a DOAC.” (P43-C-P)
“The major message from me at that point was I didn’t care what anticoagulant you used as long as you used an anticoagulant.” (P2-A-GP)

Some clinicians in health economies A and C saw the availability of DOACs as an opportunity to improve a secondary care arrhythmia clinic service and thus care of patients with AF. They described that the clinic performed cardioversion procedures (restoring normal heart rhythm using electric shocks) and patients taking warfarin were required to be within the required INR before the procedure. Clinicians involved in the service described that there were instances when INR reading was outside the desired range, and thus the procedure was cancelled or delayed. Also, it was too late to book another patient into the cancelled procedure’s slot. Procedure cancellations caused increasing waiting times for patients to receive the procedure, and the service struggled to reach targets set by the organisation. Patients taking DOAC therapy did not need INR monitoring, and the procedure was cancelled only when the patient missed DOAC doses in the four weeks before the procedure. Clinicians involved in the service observed a reduction in procedure cancellations with the use of DOACs. Some noted that the improvement seen in the cardioversion service encouraged others to use DOACs in patients awaiting catheter ablation as well.

“We had a big problem with cardioversions this was the main thing, and it is all about these pathways and people were breaching on these pathways because we couldn’t get them in because their INRs were all off. What you find is you’d have today as cardioversion day; you need the blood taken within 48 hours so we might find out on Thursday that their INR was out and it was too late to get somebody else in. We would have empty slots, and it would just affect the service really … it [DOAC] turned the service round, the waits came down, we weren’t pushing people back.” (P34-C-N)

Furthermore, some clinicians commented that with the use of DOACs, there was a reduced delay in receiving anticoagulation. As some described, before the availability of DOACs patients requiring anticoagulation were referred to the warfarin monitoring service for warfarin initiation. Thus, patients had no anticoagulation to prevent potential AF-related stroke whilst waiting to be seen in the warfarin clinic or DOAC clinic (health economy B only).
“There’s no point in delaying an effective treatment if you’ve made the diagnosis and you’re comfortable to start the treatment, you should get on and treat them and not add in an unnecessary delay where they’re going to have a stroke in the next two weeks.” (P17-B-N)

Some discussed that structure of existing clinical services supported the use of DOACs in some health economies. In health economy A, some participants discussed DOAC therapy had already been used in primary care for deep vein thrombosis treatment via a clinical pathway. Thus, some viewed that initiating DOACs for patients with AF did not require a demanding change to the existing ways of working amongst primary care clinicians.

“I’m still convinced to this day that the big thing was to mandate it [DOAC] into another part of GP practice.” (P2-A-GP)

Some also viewed that the limited capacity of warfarin monitoring services to see increasing numbers of patients with AF triggered the use of DOACs. Some described that warfarin monitoring services in secondary care did not have the resources to see all patients promptly. The numbers of patients with AF were increasing as local initiatives focused on identifying patients with AF, thus further increasing pressure on the existing services. Some commented that long delays between a patient being referred and seen in the clinic caused concerns that patients might get strokes while waiting. Hence, some clinicians and commissioners were keen for primary care to initiate DOACs.

“Everybody’s anticoagulation service was on its knees. We didn’t have a single anticoagulation service in [the region] that wasn’t at, what they considered to be, full capacity. The work that we’d done in [health economy B] had shown that actually, their anticoagulation service was really at breaking point, it was held together by staff who were just really motivated to do right by patients, but it was massively under-resourced and under-funded and really struggling to maintain its patient load.” (P25-B-P)

However, some commented that warfarin monitoring services in secondary care were not commissioned to switch patients to DOACs and some primary care monitoring services had non-prescribing clinicians. Thus, patients were referred to their GPs with advice to switch warfarin to DOAC therapy.
“We do not commission our secondary care anticoagulation clinic to initiate or monitor DOAC prescribing.” (P43-C-P)

“They are nurse led [anticoagulation clinic] and they are not prescribers. They do not have the power. They are not commissioned to make those switches and those decisions [warfarin to DOAC].” (P31-C-P)

Others noted that there was also not enough resource within the warfarin clinic to identify all patients taking warfarin that could be switched to DOAC therapy.

“There are still a lot of people on warfarin who we would like to switch, but we have not got the resource to do that. We can’t do that with our current staffing levels and the number of prescribers we have … there is an unmet demand.” (P21-B-C)

Some decision-makers stated that the place of DOACs in the existing anticoagulation pathway was unclear in health economy B. The existing service was designed to initiate and monitor warfarin. Hence, they discussed that before making DOACs more widely available, they wanted to set up a pathway for DOAC use. Some also noted that primary care wanted a controlled introduction of DOACs with a well-defined place in a clinical pathway, which contributed to the classification of DOACs as amber (shared care) medicines. Consequently, a clinic designated for DOAC initiation was created in secondary care to facilitate the introduction of DOACs. Although some perceived the clinic to be a “good and right idea to get things moving”, others argued that it slowed down the implementation of DOACs as the new created pathway was complex and convoluted.

“If you set up a clinic like that, every patient has to go through a DOAC clinic; you are automatically creating barriers because you’re saying, well, the only way to start a DOAC is to refer to this clinic, so how are GPs going to start a DOAC then. So, if you keep it in that way, you won’t spread it out.” (P18-B-C)

However, some commented that secondary care DOAC clinic in health economy B was not equipped to see all patients eligible for DOACs. The clinic was running once a week with a small team of two prescribing pharmacists and a consultant overviewing the service. Some reported that the wait times for patients to be seen increased as the number of referrals increased. There were also reported issues with patients not attending appointments.
“The [DOAC] clinic did not work very well. There was a lot of people not turning up.” (P29-B-P)

Some stated that the recognition of the limited capacity within the clinic was another driver to explore DOACs use by primary care and introduction of “grey” classification.

“Capacity in that clinic was limited … which slowed down the implementation of using DOACs, initiation of them, which is why we looked at alternative models.” (P29-B-P)

Others also noted that at the same time, they did not want to destabilise warfarin monitoring services. Thus, some were more cautious than others with the introduction of DOACs. For instance, in the health economy B warfarin monitoring service was reconfigured and recommissioned after DOACs were introduced. Some described the new service as being more clinically responsive and efficient. Thus, a few participants commented that the improved service contributed to warfarin therapy being preferred in the health economy B.

“We’ve just been trying very hard to get the warfarin service … in a better state and improved investment to try and be able to manage patients more effectively, so there was the thought ‘well if we’ve got all this money invested on managing patients on warfarin, should we be supporting the use of something different?’” (P22-B-GP)

Others observed some GPs delivering warfarin monitoring service were slow in the uptake of DOACs. Some discussed that there was no incentive to use DOACs or switch warfarin patients because DOAC therapy monitoring was not a commissioned service like warfarin. In others opinion, it had no impact on the uptake of DOACs.

“At the end of the day GPs are small independent businesses who’ve got an NHS contract, and if they are running a service that makes a profit, they will be more likely to run that service.” (P40-C-P)

6.3.3.2 Collaborative work

This subtheme presents how collaborative work within health economies influenced the use of DOACs. Interview participants shared a consensus that the use of new medicines usually begins in secondary care before spreading into the primary care setting. Secondary care was used as a testing ground for new medicines that stakeholders had reservations about their safety and effectiveness in a real-world
setting. In health economy B, some commented that secondary care historically dominated policy decisions. The Trust was seen to have local and national leads in cardiology and cardiovascular work and thus strong clinical leadership. Hence, in their view, primary care clinicians were more likely to agree and follow secondary care decisions. However, a few participants observed a mistrust of GPs by secondary care clinicians. Contrastingly, in health economy A, GPs were described as more independent from secondary care due to the Trust having less visible clinical leadership in primary care.

“[Health economy B] general practice is different to [health economy A] general practice. So [health economy A] general practice tends to sail its own ship and determine its own destiny, and our hospital lives with that. [Health economy B] is dictated to by the behemoth that is the [Trust] and the GPs over there are much more likely to follow what they’re told to do by the hospital. When our hospital tells us to do things, we tend to take it under consideration and if we feel it’s in our patients’ or our best interest, we’ll probably do it.” (P2-A-GP)

In health economy C, some participants described forming a multidisciplinary group with primary and secondary care stakeholders to develop a joint anticoagulation guideline for patients with AF. Interviewed members of the group reflected that involvement of the “main players” (e.g. commissioners, clinicians) resulted in a high acceptance of the guideline with the increased use of DOACs within the clinical community. Some commented that they observed an increase in anticoagulation rates and a decrease in stroke incidence after the guideline with accompanied education was launched. Others perceived the successful implementation of DOACs was due to the collaborative working across the health economy.

“I think getting the involvement of the CCG … getting the buy-in involving all the main players is much more important. So, you know with DOACs it’s been a success story in [health economy C].” (P33-C-C)

Some stated that input from different stakeholders facilitated discussion about concerns of the clinical community regarding DOACs, e.g. reversibility, high cost. Also, input from different interest groups ensured the relevance of the guidance to different clinicians involved in anticoagulation of patients with AF. Others also noted that the involvement of different stakeholders opened access to resources, e.g. economic
modelling for DOAC, and clinician groups, which contributed to the success of the guideline implementation.

“Before in secondary care when we tried to go out to educate in primary care settings it was very difficult, very difficult to get into the GP Locality Meetings … because we were working as part of a consensus group and we had members of primary care in that group they then gave us access to those kinds of meetings. And that was invaluable. We’ve never been able to educate in that way before.” (P31-C-P)

In health economy B, some participants reported that some GP practices recruited pharmacists or independent providers to reduce the workload. The additional support was used to identify patients with AF who were not anticoagulated and then initiate anticoagulation therapy. Others also noted that some CCGs within the health economy delivered a short-term project to provide additional support to GP practices. During the project, the medicine management pharmacist-led team was reviewing patients with AF to increase anticoagulation use and “clear the backlog”.

“My team started doing some work to support them [GPs] and we did see quite a big jump in initiation at that stage. But again, that was only a short-term project. The idea was we’d support the backlog, then the GPs would then continue to do that. As GPs in [health economy B] weren’t used to initiating anticoagulants, there’s a bit of a learning and confidence building.” (P29-B-P)

Some participants in health economy B also commented that the GP Confederation, representing a collective view of GP practices, was formed in 2018. The GP Confederation was said to be focusing on increasing the rates of anticoagulation and use of DOACs by supporting GP practices with reviewing and identifying patients with AF requiring anticoagulation.

6.3.3.3 Activities supporting innovation

Many participants discussed the availability and delivery of local educational activities in both primary and secondary care. The educational sessions aimed to reduce the use of aspirin, raise awareness of DOACs, improve knowledge about anticoagulation in AF, increase the confidence of clinicians to initiate DOACs, and ensure safe prescribing of DOACs. Some noted that commissioners were very supportive in organising and delivering training to clinicians by utilising their medicine management
teams and expertise in the local clinical community. Also, in some health economies, educational activities were incorporated in the improvement programmes.

“We have quite a comprehensive medical and clinical education system in [health economy C]. We have something called Protective Learning Initiatives where we pay for back cover for all practitioners to come out of practices for an afternoon. We have done a topic on atrial fibrillation and anticoagulation with specialist presenting their stuff.” (P42-C-O)

Many viewed the educational activities to be pivotal in increasing the local use of DOACs by removing perceived barriers for their use, improving clinicians understanding and confidence. For instance, in training sessions concerns of bleeding with DOACs and lack of monitoring were addressed to increase clinicians’ confidence in the therapy. Others also commented that educational activities were used to spread the message of a preferred oral anticoagulant therapy within the local health economy.

“We have been involved in educational work with GPs, trying to break these boundaries down, and now GPs are less problematic about initiating and following up DOACs.” (P18-B-C)

In secondary care, some participants described how numerous educational sessions were delivered to clinicians involved in anticoagulation and care of patients with AF, e.g. doctors, pharmacists, nurses. The training was delivered by clinicians specialising in anticoagulation (nurses, pharmacists, consultants).

“In the hospital, yeah lots. So, basically there was an enormous amount of education done by the pharmacy - our own staff, pharmacists, lot of education done on the medical staff.” (P28-B-P)

In primary care, the educational sessions were delivered by both primary (GPSI) and secondary care clinicians (consultants, pharmacists). As some described, the sessions were simplified and lecture-style. Others noted sessions with clinical topic expert imparting knowledge was not sufficient to change prescribing practice. In their opinion, sessions addressing factors influencing prescribing behaviour were needed

“Simple benchmarking education won’t do it; it needs to be addressing the cognitive barriers to uptake of new stuff, so helping people to understand the consequences, helping people to manage the risk, helping people to have different conversations with their patients.” (P25-B-P)
A few commented that educational information about DOACs was also shared via GP practices' newsletters and bulletins. However, they were perceived to be of little value in increasing GPs' knowledge and uptake of DOACs.

“There’s a thing called the GP bulletin, where we pass that ... I mean, obviously the impact of that is limited …” (P37-C-GP)

Some also commented that it was difficult to educate everyone at the same time. Thus, target groups of clinicians were identified and educated. Some also noted that the delivery of educational activities varied between different health economies and CCGs within the health economy. Also, in their view, the educational activities could have been better timed, coordinated and integrated across the health economy. For instance, health economy B had three CCGs, and one CCG started training their GPs earlier than the other two CCGs. Some participants in health economies A and C described educational activities being delivered at the same time to primary and secondary care, whereas in health economy B training was provided first to secondary and later to primary care clinicians. Furthermore, interviewed community pharmacists viewed the available training to them being sporadic and probably too late. Some suggested that educational activities should have been delivered earlier, ideally at the same time as the DOACs were launched or just before the launch.

“The training needs to be more coordinated and integrated, so you know, that it was working within pharmacist GPs you know, community pharmacy and nurses and all that was working had the training at the same time; we knew what everybody was being told.” (P29-B-P)

A few clinicians stated they did not have any formal form of teaching on DOACs and instead educated themselves through their experience and continuous personal development activities in their own time. Others noted that attending one educational session was not sufficient to gain confidence in using DOACs. In their opinion, continuous educational activities would have been better. Hence, some CCGs in the health economy did a roll-out training or recorded the sessions and the recordings with presentation slides, and additional resources, like patient aids, were available online for clinicians to view in their own time. In the health economy A and C, the described activities were mostly standalone sessions.

“They [GPs] were turning up to one education session, nobody goes out of one
Feedback to clinicians on the stroke rates and the use of DOACs was also utilised to promote the use of oral anticoagulation, including DOACs. In health economy C, a commissioner described a system put in place in primary care to reduce inappropriate or incomplete referrals to secondary care. The system allowed commissioners to identify GP practices that needed additional educational support. During the process, GP referrals were monitored, and feedback with additional “in-house” training was provided to GP practices, whose referrals did not meet the required standard. As a result, some of the referrals for anticoagulation were prevented as GPs learnt to initiate the therapy themselves.

“Some information would go back to the practice with supporting information or one of the support people to help the practice developing a means of doing that themselves … we were able to pick up the quality of referrals that were being made to secondary care, and we were able to identify where there were shortcomings in the quality of the information that patients were just being handed over.” (P42-C-O)

In health economy B, some commissioners described using medicines information dashboards to encourage GP practices to increase their anticoagulation use. The dashboards showed anticoagulation rates in patients with AF for each GP practice within the health economy. In health economy C, some commissioners commented that they utilised GRASP-AF and SSNAP data to provide feedback to GPs on their anticoagulation prescribing rates to encourage further improvement and also reduce the use of aspirin for stroke prevention in AF.

“We used grasp data to give [GP] practices feedback … so they know what their anticoagulation rates are against their peers, talked about that in a lot of meetings. We gave them data on what proportion of their high-risk atrial fibrillation patients were on aspirin alone, and we drove down the aspirin alone prescribing quite considerably.” (P40-C-P)

6.3.3.4 Promoted prescribing practice

The subtheme discusses the influence of local policies, guidelines, and local commissioning statements communicated via medicine formularies on the use of DOACs within local health economies. The described impact of these elements varied
between the studied health economies. In health economy A, a couple of decision-makers described a local clinical pathway promoting warfarin as the first-line therapy, but many clinicians stated no local guidelines were specifying oral anticoagulants' preference. Some clinicians were aware that DOACs had a green traffic light classification on the local medicine formulary, meaning that both primary and secondary care clinicians could initiate them. Others did not know the local formulary status of DOACs.

“I was an independent prescriber, so I would just prescribe whatever I felt was suitable for the patient. So, I wasn't restricted to say that you're not meant to prescribe this or that.” (P5-A-P)

Furthermore, one decision-maker commented that restricting DOACs through the medicine formulary would not work as control of their prescribing was not realistic. Thus, clinicians in the health economy A reflected that they had no local restrictions when deciding between warfarin and DOACs for new patients. Although local guidelines did not state a preferred DOAC, some clinicians noted that commissioners encouraged the use of rivaroxaban.

“It is an impossible thing [formulary restrictions on prescribing] to police and control … the commissioner has zero control over what a GP does or doesn't do with FP10 pad [prescription].” (P12-A-O)

Many participants in health economy C described a similar experience with all oral anticoagulants being available to prescribe and DOACs having a green traffic light classification. Contrary to health economy A, participants in health economy C described the availability of a joint primary and secondary care guideline for oral anticoagulants in patients with AF. As some clinicians described, the guideline was developed by primary and secondary care clinicians and advocated the choice of therapy that was the best for the patient. Thus, many participants stated that they experienced no local restriction on the use of DOACs and were able to offer patients different therapy options.

“I think we bent over and backwards in [health economy C] to not only offer DOACs but to offer all the DOACs and to have informed discussions with patients about which DOAC they might like …” (P40-C-P)
Before the joint guideline publication, several participants recalled a regional guideline advocating warfarin as the first-line therapy. Still, local clinicians largely ignored the recommendation as there was no policing of adherence to the recommendation. Additionally, the guideline was developed outside the organisation and did not agree with the organisation’s view on the use of DOACs.

“We weren’t very keen on this warfarin first, rivaroxaban second approach, that had been cooked up elsewhere, it wasn’t something that we particularly agreed with within the specialists in [Trust]… it was officially our guidance, but not really what we followed.” (P36-C-P)

In health economy B, many clinicians described that local guidelines, before the release of NICE AF management guideline, advocated warfarin as the first-line therapy. Most participants noted that although all oral anticoagulants were available, DOACs use was restricted through the local medicine formulary conditions. DOACs were briefly classed as red (for secondary care use only) and then as amber shared-care medicine (for secondary care initiation and continuation in primary care). The amber classification limited the initiation of DOACs by primary care clinicians.

“There [health economy B] were lots of barriers to using it [DOACs]; you really had to spell it out why the patient couldn’t have warfarin. It had to be manipulated sometimes to get them onto a DOAC and to keep them on it.” (P1-A-N)

As some GPs wished to use DOACs, a grey (primary care can initiate for low-risk patients) classification was later added to the formulary, enabling them to do so. Although warfarin preference was removed from local guidelines to align with the NICE recommendations, some clinicians commented that there was still a preference for warfarin. However, others commented that there was a change in prescribing practice with more clinicians preferring DOACs over warfarin. Some also commented that when choosing between DOACs, there was initially consensus for rivaroxaban to be preferred over others.

“Initially, with the DOACs, we classified them as amber. So, they’re all initiated by secondary care … probably a year after NICE came out and we changed the classification, so it was a bit of a grey. So, if the GPs felt that they got the clinical competency to initiate a DOAC, then we would allow that to happen.” (P29-B-P)
Some decision-makers added that formal advice on conditions to use DOACs and preferred therapy was not updated promptly. Hence, some clinicians noted as they got more confident with the use of DOACs they worked around the restrictions to get patients started on DOAC therapy.

“The formal advice was slow to change, i.e., to be reissued but there was a definite drift in practice that the formal advice issued then subsequently along the way just more or less kept up with. So, actually, people if you like, developed their own practice, their own comfort with the sorts of patients who they were using the DOACs for.” (P27-B-P)

Furthermore, there was a consensus amongst participants that wholesale or automatic switching of patients from warfarin to DOAC therapy was not encouraged. Instead, as many clinicians and commissioners stated switching of patients with inadequate warfarin control was supported. Thus, some clinicians involved in warfarin monitoring service described in-house guidelines on when to inform and offer patients taking warfarin about DOACs in line with the NICE AF management guideline.

“They [commissioners] didn’t want to see a wholesale switching over of people.” (P17-B-N)

6.3.4 External health system context

This theme presents identified factors outside the studied health economic structures that influence prescribing and policy decisions. The theme is presented in three subthemes: national directives, NHS restructuring, and commercial influence.

6.3.4.1 National directives

This subtheme presents national policies, directives, and representation of patient voice that had an impact on the implementation and use of DOACs within studied health economies. A few participants discussed the impact of changes in the Quality and Outcomes Framework (QOF). The QOF is part of the general medical services contract and is thus linked with GP practices' income. The updated QOF promoted the use of anticoagulation by changing stroke risk calculation (i.e., CHADS2 to CHA2DS2-VASc) and removing aspirin for stroke prevention in patients with AF. Hence, they viewed that GPs had the incentive to ensure their patients were on appropriate anticoagulation to receive the allocated QOF payments.
“What the read cruncher was, was the change to QOF, so QOF changed and said: ‘CHA₂DS₂-VASc, not CHADS₂, no aspirin. Anticoagulate.’ and gave it a lot of money, so there were a lot of points riding on AF in QOF and if you look at where QOF changes you see the line suddenly flick and we started to anticoagulated properly.” (P2-A-GP)

One participant also highlighted that GP practices used QOF reports to identify where they were not meeting the QOF requirements and which patients were due for clinical review. As aspirin was removed from QOF parameters, the reports highlighted patients with AF on aspirin as not being anticoagulated for GPs to target.

“It [anticoagulation] appears in the QAF report, so you know that they [GP practices] have the mock-up reports, they check that they’re not getting the points for … suddenly all those non-anticoagulated patients were appearing in a printed-out list that they didn’t previously have.” (P42-C-O)

According to many participants, NICE recommendations shaped commissioning and prescribing decisions. Some participants noted that local discussions about the DOACs use for patients with AF were taking place before the NICE evaluation of DOACs was available. However, they agreed that NICE approval of DOAC therapy facilitated its implementation within the health economy.

“NICE endorsement … is really, really key. People won't act really without NICE guidance.” (P44-P1)

Some also highlighted organisations had a statutory obligation to implement medicines that had a positive NICE Technology Appraisal (TA). Therefore, once NICE TAs recommended DOACs, they were available for use within the health economy. Others discussed that NICE TAs did not specify DOACs place in existing clinical pathways. Therefore, decisions, where the recommended medicine fitted within the existing clinical pathway, were made locally, which was reflected in local guidelines and medicine formularies.

“I think the issue with the DOACs when they came out was that it wasn’t just about having the medicine available on the formulary and saying ‘yes you can have it’. It was a whole pathway change because … the whole pathway was about warfarin.” (P26-B-P)
Also, others noted that the impact of NICE guidelines on commissioning decisions differed to NICE TAs as they were "aids to help people to deliver good quality care" and not legally binding. However, the commissioned organisations were expected to comply with the guideline. Therefore, some decision-makers and commissioners highlighted that the NICE AF management guideline was interpreted differently by different people in the studied health economies. Some participants, in particular in health economy C, perceived that all four DOACs should be available for patients to choose from. Others translated NICE recommendations into offering a choice between warfarin and DOACs, meaning that what DOAC(s) could offer could be decided at the local level. In all health economies, some participants stated that their recommendations were in line with the NICE AF management guideline.

“How do we interpret what the NICE guidance is? Providing patients can access a DOAC, the actual specific DOAC which you choose at the point of prescribing, can that be decided at a local level?” (P38-C-P)

“How do you offer an equivalence? Well, if NICE say it’s one of a range, you have to choose from the range, don’t you? So, you have to pick the first-line choice. You can’t get into a conversation with a patient and say: ‘Which name do you fancy?’” (P23-B-P)

Others were not certain if after the publication of the NICE AF guideline commissioners could state a preferred DOAC. Hence, some participants critiqued the guideline for giving all four DOAC agents equal weight and not indicating that decisions on a preferred DOAC agent could be made locally. Some argued that a preferred DOAC therapy option should be decided locally. Otherwise, the purpose of having a local medicine formulary was meaningless.

“In the beginning, there was a leniency to try and have just one DOAC on the market or one preferred DOAC in that it was deemed that that would be safer … because of the NICE guidance suggesting that patients should have a choice, that then quickly got thrown out if you like.” (P31-C-P)

Despite different interpretations of the guideline, many participants commented on local recommendations on DOACs use, and prescribing behaviour changed after the guideline’s publication. Some highlighted that the NICE AF management guideline changed stroke risk calculation and removed aspirin from recommendations, which
was another push for the use of anticoagulants. Others also commented that most local restrictions to DOAC therapy use stipulated in local policies and formularies were removed. Some participants viewed NICE AF management guideline having a greater weight in decision-making than local policies as NICE was perceived to indicate the best practice.

“Once NICE has issued that guidance then no local area restrictions are going to trump and supersede that guidance because it's within NICE, so it's appropriate to offer it, and if they choose, it's appropriate to give them whichever one they want.” (P17-B-N)

Furthermore, in the opinion of some participants, the NICE AF management guideline gave more confidence to prescribers to use DOACs. In health economy B, a clinician working in the DOAC clinic observed a high increase in the referral of new patients diagnosed with AF by their GPs.

“[There was] a big flood of referrals into our clinics when NICE guideline was published for patients who were not already anticoagulated.” (P21-B-C)

Some also reflected that NICE TAs assessed the cost-effectiveness of the medicine, and guidelines stated the best practice, but they did not consider implications for CCGs. As some discussed, local commissioners were expected to discuss financial implications on local health services and ways to implement the recommendations. One stakeholder critiqued local implementation of NICE TAs because people tended to read only the guidance summary (section 1 of TA) and not the consideration of evidence (section 4 of TA), which in the case of DOACs provided arguments for justifying well-controlled warfarin preference as the first-line therapy. Others noted that information to support local implementation of DOACs came later, e.g. NICE implementation collaborative, and were deemed impractical due to requiring a “huge amount of capacity” to use it. Also, some discussed that they did not know how to evaluate if the implementation of NICE guidance was successful because it was self-reported. Hence, some suggested that providing supporting information or tools on implementing DOACs in practice at the same time the guideline was published would have been more beneficial.

“They tend to say what should happen and then they leave it to NHS England and CCGs and providers to argue about the costs and the help.” (P2-A-GP)
A few participants mentioned several patient organisations (AF Association, Arrhythmia Alliance, Stroke Association, and local patient groups) that were perceived to exert influence on patients’ therapy choices and clinician’s prescribing behaviour. The patient organisations were seen increasing awareness and knowledge of patients about DOAC therapy. Consequently, informed patients were enquiring about DOAC therapy in consultations with clinicians, driving the use of DOACs.

“A lot of them, if they’ve gone on the Arrhythmia Alliance or other websites, on there, it’s about anticoagulation. Some of them are quite clued up on things, really.” (P34-C-N)

Some also stated that patient organisations, e.g. AF Association, Arrhythmia Alliance, were working with local clinicians to support education and awareness about DOACs of clinicians. These organisations had a positive outlook on DOACs and aimed to increase the uptake of DOACs.

“There was a great drive, a lot of it through [GPSI] work with the AF association meeting in [health economy A].” (P39-C-C)

6.3.4.2 NHS restructuring

Some participants discussed the changes occurring in the funding and provision of NHS services, i.e., restructuring, affecting the implementation of DOACs. For instance, some participants in the healthcare economy B reflected that engagement with primary care could have been better. However, it was difficult as primary care was perceived to be constantly reorganising; thus, stakeholders to approach were changing. Indeed, some participants noted that at the time of DOACs introduction Primary Care Trusts (PCTs) were being replaced by GP-led organisations known as CCGs in England.

“So, it went from five PCTs [2002] to being one PCT [2007] … and when it was announced around the changes in the Health and Social Care Act … they were gearing up in terms of that CCG infrastructure … the proposals in [health economy B] came forward as three CCGs, and that was what was formed and officially took over in April 2013.” (P24-B-P)

In health economy B, some decision-makers from secondary care commented that changes due to NHS restructuring added extra complexities to the implementation of DOACs. In their opinion, it was harder and took longer than needed to reach a consensus across the health economy as more decision-makers with different
opinions were involved. One stakeholder commented that the agreement could have been reached sooner and the additional time spent in meetings resulted in avoidable use of public money that could have been used better elsewhere. Some stakeholders reflected that it was easier to work with one PCT than three CCGs.

“There [in meetings] was a lot of discussions, and a lot of influencing that was done … and it took a long time to reach an agreement about that, at a significant public cost, actually. We all earn a salary, don’t we? We go and sit in rooms in meetings; the meetings are not free, so the longer it takes to reach a consensus or to agree that the more and more that’s driving up the cost … whether that was a good use of public money I would question actually. I think we could have got there a lot earlier than we did.” (P28-B-P)

Another stakeholder held the view that people in NHS structures being changed were concerned about their continuation of employment. Thus, some decision-makers were perceived to be preoccupied with securing future employment in the reconfigured structures and might not have been as responsive to requests or as quick in decision-making. Consequently, it could have contributed to a slower implementation of DOACs compared to other health economies.

“When you have continuous reconfiguration and people at risk … people are consumed by what jobs they may or may not have … but sometimes that slows pieces of work down because people are then distracted by other continuous reorganisation, reapplication for jobs.” (P26-B-P)

Furthermore, a few participants reflected that at the time of CCGs introduction, the priority for CCGs was to complete the restructuring. Thus, some noted that in health economy B decision-makers were given more freedom on how to implement DOACs.

“We started it during times of PCTs … gave birth to CCGs during that time … they were busy being born and they had bigger fish to fry being really blunt. So, they said to us: ‘Get on and do whatever it is you need to get on and do.’” (P12-A-O)

Others noted that with the reforms of the Health and Social Care Act 2012, clinical networks aligned with commissioning networks in primary care, e.g. cardiovascular clinical network, delivering improvement projects were dissolved. Consequently, the opportunity to have discussions about DOAC implementation across different health economies in the same region was not available anymore. Also, one stakeholder noted
that policies and prescribing guidelines used by PCT, including the ones regarding the use of DOACs, required rewriting and updating for new incoming CCGs, which took several years to complete.

“PCTs which allowed us to establish policy including prescribing policy and commissioning decisions, especially around cardiovascular because we have a good cardiovascular clinical network … we developed a set of guidelines and a flow chart to help practitioners and prescribers to come to a decision on appropriate anticoagulation … all that disappeared with the new regime in CCGs. So, we then had to spend several years rewriting all the policies and prescribing guidelines for CCGs.” (P42-C-O)

6.3.4.3 Commercial influences

Many participants discussed the presence of the pharmaceutical industry at the time of DOACs implementation in the studied health economies. Some clinicians and stakeholders had a negative view of the industry. They stated that they did not see industry representatives due to lack of time, regulations, and lack of value in meeting them. Some also steered clear of pharmaceutical industry-funded educational events. In their view, pharmaceutical representatives provided biased information promoting their agent, and their aim was “to sell the drug”. Instead, they used other information sources to obtain more balanced information about anticoagulation therapies. Some also noted that although there was no official policy not to see the representatives, there was a general feeling amongst GPs not to see them.

“Too busy, we don’t have time to do our normal jobs so to sit and be advertised to just seems wrong.” (P3-A-GP)

Also, one participant shared receiving negative comments from peers due to association with industry and thus potential bias in decision-making.

“I felt very judged, and I had a few off-hand comments actually about me selling myself to pharma. I’ve not had any payment … if someone buying you a sandwich is going to influence your clinical decision, then that’s something you need to look at within yourself.” (P31-C-P)

One participant described that decision-makers in the health economy A were against a partnership with the pharmaceutical industry. Thus, a negotiated lower price for a specific DOAC was declined and instead all DOACs were made available for local use.
“[Group of opinion leaders] managed to negotiate a rebate deal to get a stonkingly good price for one of the agents … the CCG would not accept any partnership with industry and so stated in the public record that we could have all three of the currently mandated DOACs.” (P2-A-GP)

Another participant in health economy B also noted that decision-makers in primary care decided against rebates because once you accept it, competitors reduce the price of their agent. Another participant in health economy C added that they have a clear rebate policy to consider rebate offers made by the industry. However, he stated local decisions on new medicine availability consider the drug list and not the offered rebate price.

“We did not really, from primary care, we did not enter into the rebate [price concession paid by a pharmaceutical manufacturer] story because that just complicates things. I am glad we did not because as soon as people made that decision somebody else knocked the price down.” (P28-B-P)

Although there was a consensus that the industry provided biased information, some clinicians valued the simplified presentation of it, access to unpublished research data, and information on what is coming next and what other health economies were doing. They argued that the industry did not influence their decisions as they were trained to appraise the evidence critically. Some were also more receptive to resources available from the industry as funding and resources within the NHS were limited. They argue that the industry resources were used to support achieving the organisation’s aim of increasing anticoagulation rates. Some stated that received sponsorship for venue and refreshments contributed to the willingness of people to join a working group outside working hours in health economy C. Other clinicians commented that they cooperated with the industry in delivering educational sessions but stated that the industry did not influence their views and presentation at the education events. Others also used patient information provided by the industry, e.g. leaflets, booklets, learning about DOACs. Some also reflected that working with industry-linked them with national experts, facilitated discussions between primary and secondary care, and increased confidence in using DOACs.

“I think in this particular area the fact that the drug companies want to increase the number of people taking their product I think nicely aligns with the fact that I want
everyone who is appropriate and who has a thrombotic risk and they have to be on an appropriate anticoagulant. I think you can align those aims and use the resources in the pharmaceutical companies to improve the communication, to have patient information leaflets, to have educational events for GPs.” (P33-C-C)

Partnerships with the pharmaceutical industry were also formed in health economy B. Some described that funding was obtained from the industry to support the redesign of the existing warfarin monitoring service. The funding was used to recruit a project manager from an independent company to manage the redesign project as required expertise and time resource was not available in the Trust. Steps were undertaken to ensure the industry did not influence the redesign of the service, e.g. independent company recruited, all pharmaceutical companies having DOACs contributed. Some commented that the partnership resulted in quicker completion of the service transformation, but it did not increase the uptake of DOACs.

“That didn’t quite get the results that we wanted, but it got far enough, and I do believe it went further and faster because there was extra capacity in the system to do the transformation, which was delivered by boots on the ground from pharma people. I don’t think that actually made a material difference in opening the doors to the DOACs.” (P25-B-P)

Furthermore, one of the three CCGs in health economy B had industry-funded third-party companies to support some GP practices experiencing issues with capacity and expertise to review the anticoagulation needs of patients with AF. The funding provided clinicians (consultants, pharmacists, nurses) not associated with the industry to assess patients with AF for anticoagulation and switch patients on warfarin to DOAC therapy where indicated. Although the partnership delivered increased anticoagulation rates, it did not leave a legacy of competence and confidence amongst GPs. The anticoagulation rates plateaued after the funding has finished. Also, some described concerns with the quality of some of the clinics but noted it was expected. Others commented that there were GP practices not willing to work with the pharmaceutical industry and some GP practices were keen to have additional support. In health economies A and C, funding from industry for such clinics was not utilised.

“The quality of some of those clinics and the quality of the consultant recommendations caused some concern, but I think it is always very difficult when you
Many participants acknowledged that the pharmaceutical industry tried to influence local prescribing and commissioning decisions. Some discussed that the pharmaceutical industry did not influence policy decisions directly. They were not part of the decision-making and were not taken notice of during the decision-making process. Instead, they exerted indirect pressure to use their agent by increasing attention to DOACs. Some added that DOAC therapy in AF was a long-term indication. Thus, the industry was very keen for clinicians to use them and “lots of money to be made”. The pharmaceutical industry was described as using discount offers for their agent, supporting educational meetings, providing patient printed information leaflets, commissioning medical writers to write about DOACs in national media, using social media to advocate that their agent is better than another and warfarin, helping to run All-Parliamentary groups, and spreading the message that innovative medicines are not used in the NHS.

“There has been pressure in the background all the time; they’re very present, things like discounts, that’s obviously pressure to use their agent. They are always there at educational meetings if pharma is allowed. Then there’s the tedious story about which one’s best. And I’m pretty sure that they’d be behind some of the key markers and drivers for the story about Warfarin/DOAC balance, not using innovative medicines.” (P23-B-P)

“Is the pharmaceutical industry exerting some influences? They definitely are, but I would say they are around the periphery of the core decision-making. But they are definitely there.” (P27-B-P)

Some commented that interactions with representatives have changed over time. Some stated that at the beginning, they had a negative experience and described representatives as “aggressive” and “unpleasant”, thus creating an antagonising relationship with them. However, it has changed over time as representatives are more interested in how they can support clinicians to implement their promoted agent.

“They definitely made their presence known and weren’t always that pleasant … I had experiences with them about why I was using this drug and why I was choosing this drug and things. I think they have moved on a lot since then. It’s a lot more about
‘How can we help you; how can we support you?’ now rather than ‘What you using that drug for?’ which I found uncomfortable, obviously.” (P16-B-P)

6.3.5 Comparison: healthcare professionals’ and key stakeholders’ perspectives

Although there were similarities between views of healthcare professionals in patient facing roles and key stakeholders in non-patient facing roles, subtle differences were also noted (Figure 6.2). Both participant groups discussed real-world effectiveness, safety, and the practical convenience of DOACs. Healthcare professionals focused more on initiating and monitoring aspects of anticoagulation and convenience to patients. Also, healthcare professionals discussed in depth patient factors, e.g. involvement in decision-making, that influenced their prescribing decisions, whereas key stakeholders discussed more the benefits of DOACs related to existing anticoagulation services or local organisation overall. Also, both groups discussed the unit cost, monitoring and direct health impact costs, e.g. bleeding, stroke, of DOACs and warfarin, key stakeholders focused more on system costs and the financial impact of DOACs on local health budgets and their management.

Participants from both groups highlighted barriers and enablers related to healthcare professionals’ experience with and knowledge of anticoagulation and the influence of their peer-network. Healthcare professionals discussed their oral anticoagulation therapy preferences and how these preferences were shaped by their colleagues and locally promoted therapy preferences, e.g. through local guidelines, and key stakeholders highlighted the significance of opinion leaders and local champions on formulating local guidelines, and clinicians’ prescribing behaviour.

Differently to healthcare professionals, key stakeholders discussed more the local implementation process by identifying collaborative working across primary and secondary care settings and the negative effect on continuous NHS restructuring. Also, key stakeholders emphasised the importance of national directives such as NICE TAs and changes in QOF on their decisions and uptake of DOACs. Lastly, both groups acknowledged the influence of the pharmaceutical industry on prescribing decisions and the uptake of DOACs. However, their views were mixed with some participants identifying positive aspects of pharmaceutical industry involvement in promoting local use of DOACs and others had more reserved or even negative view.
6.4 Summary

This chapter has provided an in depth analysis of healthcare professionals’ and key stakeholders’ views on the barriers and enablers to the uptake of DOACs for stroke prevention in AF across three different health economies. While this section summarises the findings, the full discussion of the results is presented in the Chapter 8.

While there were similarities and differences in the process of implementing DOACs across the studied health economies, altogether the participant narratives reveal a number of factors influencing the DOAC uptake that have not been previously reported. The findings of this chapter are summarised below and the discussion of the findings is presented in Chapter 8.

The findings indicate that participants’ perception of the value of the innovation influenced their decisions to support or not the local uptake of DOACs. Participants discussed real-world evidence or lack of it and how it influenced their decision-making regarding DOACs. Real-world effectiveness and safety data collected locally assured some participants and thus had a positive impact on the uptake of DOACs. Educational activities were also described to have a positive impact, especially for participants who had concerns regarding the management of DOAC adverse effects, e.g. bleeding, or lack confidence and experience in using DOACs.

The high price of DOACs was suggested to be a barrier for their use, which agreed with findings from the patients’ interviews in Chapter 5. Some commissioners were concerned with the anticipated high expenditure for these medicines within limited local medicine budgets. Others considered associated monitoring (lack of it) and reduced direct health costs, e.g. savings from stroke prevention, thus supporting increased DOAC use. Nevertheless, others argued that well-controlled warfarin was more cost-effective than DOACs and additional expenditure for DOACs had a negative impact on available funding for other services needed by the local population such as mental health or social care services. Also, some discussed that the economic benefits of using DOACs were difficult to demonstrate as benefits were not seen immediately and spending/savings were scattered across different local health economy budgets. On the other hand, most participants agreed that DOACs offered greater convenience
for patients, prescribers, and the health system over warfarin, which encouraged their use in practice.

The findings indicated that prescribers’ previous experience with anticoagulation or DOACs facilitated the DOAC uptake, whereas lack of knowledge and experience with managing anticoagulation acted as a barrier. Some prescribers identified that their prescribing practice was influenced by their peers within their close working environment or the health economy. Secondary care clinicians were suggested to influence primary care prescribing. Patient factors, which included clinical characteristics and therapy preferences, also shaped prescribing decisions. Clinical characteristics were used to determine the appropriateness of DOACs. Patient involvement in decision-making allowed patients to express their therapy preferences, which encouraged prescribers to use DOACs more.

The DOACs alignment with the health economies’ priorities and existing services affected their uptake. At the time of DOACs introduction, commissioners and clinicians in all health economies were focused on increasing anticoagulation rates for patients with AF, which supported the use of DOACs. However, in some health economies, DOACs fitted better with the existing services than in others. In some health economies, DOACs were seen as an opportunity to improve current services and thus participants were keen to use them. Also, in some areas, DOAC introduction blended more easily with the existing anticoagulation services. Contrary, in one health economy a new clinical pathway or service was designed, which was perceived to hinder the uptake of DOACs. Some participants discussed collaborative work and forming partnerships to facilitate the uptake of DOACs and the success of those partnerships varied across health economies. Another factor identified to influence the uptake of DOACs was their local medicine formulary status. In areas where the use of DOACs was restricted through the local commissioning statements or guidelines, prescribers were less likely to use DOACs. However, the formulary status of DOACs was influenced by the views of commissioners and clinicians, and the willingness of clinicians to use DOACs in their practice.

Several factors influencing the DOAC uptake were linked to the external health system. Many participants put high importance to national guidelines, policies, and commissioning statements when making commissioning and prescribing decisions. National directives encouraging the use of DOACs facilitated the local uptake of
DOACs. Changes in national recommendations caused changes to local commissioning and guideline statements, leading to removal or reduction of local barriers for DOACs use. Some participants commented that continuous restructuring of the NHS, especially primary care, hindered or slowed the uptake of DOACs in some health economies. The continuous restructuring was identified to hinder collaborative work across primary and secondary care.

Participants also discussed the influence of the pharmaceutical industry on the uptake of DOACs. The pharmaceutical industry was described exerting influence through indirect and direct marketing to clinicians, partnership working with local health economies, and providing resources limited within the NHS. In some participants' views, working with the pharmaceutical industry brought benefits to all parties concerned (patients, clinicians, pharmaceutical industry) and facilitated the uptake of DOACs. Others had a more negative view of the industry and had limited or no engagement with them.

6.5 Strengths and limitations

The findings and transferability of findings to different settings should be considered in the context of the study strengths and limitations. The main strength of this study was a moderate and diverse sample in terms of participants' roles, responsibilities, settings. Participants were also recruited from three health economies with different anticoagulation service provision models (see Chapter 4). It allowed the collection of rich data, enabling greater insight into potential barriers for the DOAC uptake. Lastly, data analysis robustness was ensured by more than one researcher being involved in the process and development of themes and subthemes (see Chapter 4).

The main limitation of the study was relying on participants' accounts of events and experiences when DOACs were introduced, which could be affected by recall bias. Participant validation, which could have increased the internal validity of results, was not undertaken. Instead, the findings were further discussed with two supervisors, who were involved in anticoagulation service provision, to ensure all expected factors affecting the uptake of DOACs were captured.

This chapter has described barriers and enablers to the uptake of DOACs identified from healthcare professionals' and key stakeholders' perspectives. The following chapter will propose recommendations for improving the uptake of new medicines in
practice by mapping findings from the previous chapter (5) and this chapter (6) onto the Diffusion of Innovations in Service Organisations model.
Chapter 7 Proposal of toolkit components to facilitate the uptake of new medicines in clinical practice

7.1 Introduction

The qualitative analysis of perspectives of patients, healthcare professionals, and key stakeholders are presented in Chapter 5 and Chapter 6, respectively. This chapter sets out how the factors affecting the uptake of DOACs identified in the qualitative findings, systematic review (Chapter 2) and narrative review (Chapter 3) were taken and mapped to the elements of the Diffusion of Innovations in Service Organisations model (Greenhalgh et al. 2004). This allowed identification and development of components which may comprise a future toolkit aiming to facilitate the uptake of cost-effective new medicines into clinical practice. The toolkit, aimed at clinicians and local organisation decision-makers, sets out to provide practical recommendations that could support the uptake of new medicines. The methods used to identify potential components for a toolkit are described in detail in Chapter 4.

The following sections of this chapter describe the results of mapping the findings of this thesis on the elements of the model and identifying components of the future toolkit development.

7.2 Results

7.2.1 Mapping of the identified factors to the model

The mapped identified factors from qualitative and review findings are presented in Table 7.1. Thirteen elements of the Diffusion of Innovations in Service Organisations model had no factors identified from the empirical or literature review findings and were excluded from inclusion in the component development of the future toolkit. Also, some elements of the model in the context of the uptake of new medicines were perceived to overlap, which has been highlighted by Cook et al (2012) as well. In such instances, the mapped factors were reported only under one of the overlapping model’s elements. For instance, “compatibility” of the innovation was thought to be somehow similar to “innovation-system fit”. Both of these elements refer to the alignment of the innovation with the values and goals of adopter (clinician or organisation). The researcher also identified that eight elements of the model with factors mapped from the empirical or literature review findings were potentially not applicable to the toolkit. These elements were discussed with the members of the supervision team (BF, KS,
SR). An agreement was reached to exclude six out of the eight elements as presented in Table 7.2.

Some factors identified from empirical and literature review findings were not considered by the model. These factors were thematically grouped into three themes (Table 7.3):

- New medicine cost
- Patient factors
- Patient involvement in decision-making

The new medicine cost included the consideration of the marketing price of new medicine, associated costs (e.g. monitoring), and its cost implications for the health service (e.g. direct health outcome savings, opportunity costs). Earlier research noted that the model did not consider the costs of the innovation (Cook et al. 2012; Damschroder et al. 2009). Patient factors theme comprised of patient clinical characteristics and new medicine’s compatibility with patient’s daily life. The Diffusion of Innovations in Service Organisations model focuses on the adopter being a healthcare professional or healthcare organisation and it is thought not to consider patient needs (Damschroder et al. 2009; Nilsen 2015). The patient involvement in decision-making theme comprised of patient knowledge about therapy options, involvement in decision-making, and therapy preferences. The role of a patient is not explicitly addressed in the Diffusion of Innovations in Service Organisations model (Damschroder et al. 2009; Nilsen 2015). Although patient influence could be broadly linked to some elements of the model (e.g. social networks, decision-making), a more distinct recognition of patient role in the uptake of new medicines is needed.
Table 7.1 Empirical and literature reviews findings mapped to the Diffusion of Innovation in Service Organisations model (Greenhalgh et al. 2004).

<table>
<thead>
<tr>
<th>Elements of the model</th>
<th>Operational definition by Cook et al. (2012)*</th>
<th>Factors taken from empirical findings</th>
<th>Factors taken from literature reviews</th>
<th>Potential component for a toolkit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Theme: subtheme</td>
<td>Factors</td>
<td></td>
<td></td>
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<tr>
<td>Relative advantage</td>
<td>Degree to which the innovation is considered superior to existing practices</td>
<td>Oral anticoagulants knowledge: effectiveness (P)</td>
<td>Barrier: -Uncertainty of new medicine effectiveness</td>
<td>Real-life effectiveness</td>
</tr>
<tr>
<td>Compatibility</td>
<td>Innovations’ consistency with existing values, experiences, and needs of adopter and system</td>
<td>See Innovation-system fit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complexity</td>
<td>Level of difficulty to understand and use the innovation</td>
<td>Impact on daily life: monitoring and dosing changes (P)</td>
<td>Facilitator: -Simple dosing regimen -No frequent monitoring like with warfarin -Challenges meeting monitoring needs of established therapy</td>
<td>Complexity of use</td>
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213
| Oral anticoagulants Knowledge: safety concerns (P) | **Barrier:**  
- Deficiencies in understanding monitoring needs for new medicine by both patients and clinicians | **- Reduced monitoring and clinic visits**  
**- Complex initiation process** |
| --- | --- | --- |
| **Value of innovation: practical convenience (HCPs&KS)** | **Barrier:**  
- Complex or confusing dosing  
- Not compatible with compliance aids  
**Facilitator:**  
- Simple dosing regimens  
- Minimal dose changes  
- Less frequent monitoring than with warfarin  
- Low complexity process to initiate | **- Ease of taking and using DOACs**  
**- Complex dosing regimen**  
**- Patient adherence to required monitoring** |
| **Value of innovation: real-life effectiveness (HCPs&KS)** | **Barrier:**  
- Risk of incorrect doses being prescribed, e.g., not adjusted for renal impairment | 
| **Local health economy readiness for change: innovation-health economy fit (HCPs&KS)** | **Barrier:**  
- Complex and convoluted pathway created for new medicine use | 
| **Trialability** | Ability to experiment with the innovation on a limited or trial basis | None identified |
| **Observability** | Innovations’ results are observable to others | Value of innovation: safety profile (HCPs&KS)  
**Barriers:**  
- Adverse effects reported by patients  
**Facilitators:**  
- Good tolerability by patients | **- Patient adherence to therapy**  
**- Patient satisfaction with new medicine** |
| Local health economy readiness for change: activities supporting innovation (HCPs&KS)  
**Facilitator:**  
- Feedback to clinicians of new medicine impact on direct health outcomes | | 
<p>| <strong>Potential for reinvention</strong> | Ability to refine, elaborate and modify the innovation | None identified |</p>
<table>
<thead>
<tr>
<th>Risk</th>
<th>Risk or uncertainty of outcome associated with the innovation</th>
<th>Oral anticoagulants Knowledge: safety concerns (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Side effect profile</td>
<td>Barriers:</td>
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<tr>
<td></td>
<td></td>
<td>- Uncertainty over adverse and long-term effects</td>
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<tr>
<td></td>
<td></td>
<td>- Lack of required monitoring</td>
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<td></td>
<td>Facilitator:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Experiencing or social network members reporting adverse effects with established therapy</td>
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<td></td>
<td>Value of innovation: safety profile (HCPs&amp;KS)</td>
<td>Barriers:</td>
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<tr>
<td></td>
<td></td>
<td>- General anxiety with new medicine use due to safety issues with past innovations</td>
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<tr>
<td></td>
<td></td>
<td>- New medicine classed as high-risk medicine</td>
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<tr>
<td></td>
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<td>- Concerns with the risk of adverse effects and their management</td>
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<td>- Lack of reversal agent</td>
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<td></td>
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<td>- Concerns about unknown long-term effects</td>
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<td></td>
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<td>- Lack of frequent monitoring like with warfarin</td>
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<td></td>
<td>Facilitators:</td>
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<tr>
<td></td>
<td></td>
<td>- Real-life data not showing an increase in the rate of adverse events</td>
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<td></td>
<td></td>
<td>- Assurance and explanation to patients about risks of adverse event</td>
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<td></td>
<td></td>
<td>- Patients experiencing adverse events with established therapy</td>
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<td></td>
<td>Safety profile</td>
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<tr>
<td></td>
<td></td>
<td>- Uncertainty over adverse and long-term effects</td>
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<tr>
<td></td>
<td></td>
<td>- Safety concerns communicated in the scientific literature</td>
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<tr>
<td></td>
<td></td>
<td>- Lack of reversal agent to manage bleeding</td>
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<table>
<thead>
<tr>
<th>Task issues</th>
<th>Concerns about the innovation that need to be focused on to accomplish implementation</th>
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<tbody>
<tr>
<td></td>
<td>See Complexity</td>
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<table>
<thead>
<tr>
<th>Nature of knowledge</th>
<th>Information about the innovation can be codified and transferred from one context to another</th>
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<tbody>
<tr>
<td></td>
<td>Sociological influences on clinician prescribing: clinician capability (HCPs&amp;KS)</td>
</tr>
<tr>
<td></td>
<td>Facilitator:</td>
</tr>
<tr>
<td></td>
<td>- Knowledge and experience in using new medicine for different indication is relevant</td>
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<tr>
<td></td>
<td>- Amount of new information to be acquired</td>
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<tr>
<td></td>
<td>Education and training</td>
</tr>
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<table>
<thead>
<tr>
<th>Technical support</th>
<th>Available support components (e.g., training, manuals, consultation help desk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value of innovation: safety profile (HCPs&amp;KS)</td>
<td>Facilitators:</td>
</tr>
<tr>
<td></td>
<td>- Availability of local protocols to manage complications of new medicine</td>
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<td></td>
<td>- Availability of local protocols stating monitoring requirements</td>
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<td></td>
<td>- Availability of local clinical guidelines</td>
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<td>- Availability of clerical staff</td>
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<td>- Availability of additional supporting services</td>
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<td></td>
<td>Local protocols and guidelines</td>
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<tr>
<td>Sociological influences on clinician prescribing: clinician capability (HCPs&amp;KS)</td>
<td><strong>Barrier:</strong>&lt;br&gt;-Lack of opportunities to develop required skills</td>
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<tr>
<td>Sociological influences on clinician prescribing: peer-network influence (HCPs&amp;KS)</td>
<td><strong>Facilitator:</strong>&lt;br&gt;-Available clinical advice from experienced peers on using a new medicine</td>
</tr>
<tr>
<td>Local health economy readiness for change: activities supporting innovation (HCPs&amp;KS)</td>
<td><strong>Barriers:</strong>&lt;br&gt;-Lack of integration and co-ordination of educational activities across the health economy&lt;br&gt;-Educational activities delivered after the launch of new medicine&lt;br&gt;-No continuous educational support&lt;br&gt;-Educational activities limited to the target group of clinicians</td>
</tr>
</tbody>
</table>

**Adopter characteristics**

<p>| Needs | Observed or experienced deficit in an adopter’s practice or organisational setting | See Tension for change |  |
| --- | --- | --- |  |
| Motivation | Adopter’s interest and willingness to learn new things | Value of innovation: safety profile (HCPs&amp;KS) | <strong>Barrier:</strong>&lt;br&gt;-Perceived to be specialists’ role to initiate new medicine | <strong>Roles and responsibilities</strong>&lt;br&gt;-Lack of confidence |  |
| Sociological influences on clinician prescribing: clinician capability (HCPs&amp;KS) | <strong>Barrier:</strong>&lt;br&gt;-Lack of confidence |  | Education and training |</p>
<table>
<thead>
<tr>
<th>Values and goals</th>
<th>What adopters place value in and what are their intended goals for treatment</th>
<th>Clinician-patient encounter: perceived roles (P)</th>
<th>-Patients believed and expected clinicians would make the best and right decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sociological influences on clinician prescribing: clinician capability (HCPs&amp;KS)</td>
<td>-Selection of therapy that is the best for patient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local health economy readiness for change: promoted prescribing practice (HCPs&amp;KS)</td>
<td>-Local guideline advocating therapy choice that is the best for patient</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patient-centred care</strong></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Skills</th>
<th>Adopter’s context specific skill set</th>
<th>Clinician-patient encounter: prescribing habits (P)</th>
<th><strong>Barrier</strong>: -Perceived lack of knowledge about new medicine by clinicians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sociological influences on clinician prescribing: clinician capability (HCPs&amp;KS)</td>
<td><strong>Barriers</strong>: -Lack of knowledge about new medicine or medicines from the same therapeutic class -Lack of experience in using new medicine and/or medicines from the same therapeutic class</td>
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<tr>
<td><strong>Education and training</strong></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Learning style</th>
<th>Adopter’s consistent patterns in perceiving, remembering, judging, and thinking about new information</th>
<th>External health system context: commercial influences (HCPs&amp;KS)</th>
<th>-Clinicians avoiding industry sponsored educational activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local health economy readiness for change: activities supporting innovation (HCPs&amp;KS)</td>
<td>-Self-directed learning -Learning from experience</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Education and training</strong></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Locus of control</th>
<th>Adopter’s belief that events are under one’s personal control (internal) or that events are</th>
<th>None identified</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>None identified</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolerance of ambiguity</td>
<td>Adopter's ability to accept uncertainty</td>
<td>Clinician-patient encounter: prescribing habits (P)</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------------------------------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>Sociological influences on clinician prescribing: patient factors (HCPs&amp;KS)</td>
<td><strong>Barrier:</strong> Clinician favouring new medicine over established therapy</td>
<td></td>
</tr>
<tr>
<td>Knowledge-seeking</td>
<td>Adopter’s autonomous efforts to attain knowledge/ information</td>
<td>Local health economy readiness for change: activities supporting innovation (HCPs&amp;KS)</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>Tenure</td>
<td>Length of employment in setting and in field</td>
<td>Clinician-patient encounter: prescribing habits (P)</td>
</tr>
<tr>
<td>Cosmopolitan</td>
<td>Adopter’s strong connections with professional network; Engagement and attendance at professional meetings and other informational venues</td>
<td>External health system context: commercial influences (HCPs&amp;KS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>External health system context: NHS restructuring (HCPs&amp;KS)</td>
</tr>
<tr>
<td>Communication and Influence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social networks</td>
<td>Structure and quality of social network, both formal and informal</td>
<td>Oral anticoagulant knowledge: awareness of therapy options (P)</td>
</tr>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Sociological influences on clinician prescribing:</td>
<td><strong>Facilitators:</strong> Peer adoption and positive view</td>
<td></td>
</tr>
<tr>
<td><strong>Homophily</strong></td>
<td>Degree of similarity (e.g., experiences, values, social status) among providers targeted for implementation</td>
<td>None identified</td>
</tr>
<tr>
<td><strong>Peer opinion leader</strong></td>
<td>Internal member of the social network able to exert influence on providers’ beliefs and actions through representativeness and credibility</td>
<td>See Social networks and Expert opinion leader</td>
</tr>
<tr>
<td><strong>Marketing</strong></td>
<td>Process of promoting, selling and distributing a treatment</td>
<td>Local health economy readiness for change: activities supporting innovation (HCPs&amp;KS)</td>
</tr>
</tbody>
</table>
| | | Facilitators:  
| | - Pharmaceutical detailing  
| | - Direct-to-consumer marketing by pharmaceutical companies  
| | - Use of resources provided by pharmaceutical companies (e.g., printed material, funding)  
| | - Promotion of preferred medicine during educational sessions |
| | External health system context: commercial influences (HCPs&KS) |
| | Facilitators:  
| | - Promotion and recommendation by patient organisations |
| **Expert opinion leader** | Senior or high status formal authority with reputable expertise | Sociological influences on clinician prescribing: peer-network influence (HCPs&KS) |
| | | Barrier:  
| | - Opinion leader(s) in decision-making being resistant to new medicine use  
| | Facilitator:  
| | - Opinion leaders supporting new medicine use |
| **Champions** | Individuals who support and promote the innovation through its critical stages | Sociological influences on clinician prescribing: peer-network influence (HCPs&KS) |
| | | Barrier:  
| | - Lack of local champion promoting new medicine use  
| | Facilitator: | None identified |

**Facilitators:**
- Pharmaceutical detailing
- Direct-to-consumer marketing by pharmaceutical companies
- Use of resources provided by pharmaceutical companies (e.g., printed material, funding)
- Promotion of preferred medicine during educational sessions
- Promotion and recommendation by patient organisations
- Policies restricting pharmaceutical detailing
- News articles and media reports

**Barrier:**
- Opinion leader(s) in decision-making being resistant to new medicine use
- Lack of local champion promoting new medicine use

**Role of pharmaceutical industry**
- Promotion of new medicine

**Opinion leaders**
- Expert and opinion leaders view on a new medicine

**Promotion of new medicine**
<table>
<thead>
<tr>
<th>Local champions promoting new medicine use</th>
</tr>
</thead>
<tbody>
<tr>
<td>None identified</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bounder spanner</th>
</tr>
</thead>
<tbody>
<tr>
<td>An individual who is part of the work environment and part of the innovation technology (e.g., trainer in the innovation)</td>
</tr>
<tr>
<td>None identified</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>An individual who is a facilitator of change in various stages from problem identification or translation of intent into action</td>
</tr>
<tr>
<td>None identified</td>
</tr>
</tbody>
</table>

### System Antecedents for Innovation

<table>
<thead>
<tr>
<th>Size/Mature</th>
<th>Number and experience of providers; Date of programme inception</th>
<th>None identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formalisation</td>
<td>Degree to which an organisation is run by rules and procedures</td>
<td>None identified</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Complexity of the programme in terms of structure, departments, or hierarchy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinician-patient encounter; relationship continuity (P)</td>
<td><strong>Barrier:</strong></td>
</tr>
<tr>
<td>External health system context: NHS restructuring (HCPs&amp;KS)</td>
<td><strong>Barrier:</strong></td>
</tr>
<tr>
<td>- Fragmentation of care</td>
<td></td>
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<tr>
<td>- Lack of relationship continuity with a clinician</td>
<td></td>
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<tr>
<td>- Increasing difficulty and length to reach consensus with more decision-makers being involved</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Decentralisation</th>
<th>Extent to which locus of authority and decision-making are dispersed throughout an organisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local health economy readiness for change: collaborative work (HCPs&amp;KS)</td>
<td><strong>Facilitator:</strong></td>
</tr>
<tr>
<td>- Collaborative multidisciplinary working across the health economy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Slack resources</th>
<th>Actual versus spent budget and/or the total potential hours each provider is available versus actual time spent working</th>
</tr>
</thead>
<tbody>
<tr>
<td>None identified</td>
<td></td>
</tr>
</tbody>
</table>

### Absorptive Capacity for Knowledge
<table>
<thead>
<tr>
<th>Pre-existing knowledge/skills</th>
<th>Adopters’ level of pre-existing knowledge and skills</th>
<th>Sociological influences on clinician prescribing: clinician capability (HCPs&amp;KS)</th>
<th>Facilitator:</th>
<th>- Previous experience and knowledge in using medicines from the same therapeutic class as a new medicine</th>
<th>- Pre-existing knowledge of new medicine</th>
<th>- Clinician’s previous experience and knowledge in using a new medicine</th>
<th>- Clinicians classed as early adopters in the past</th>
<th>Existing skillset and knowledge of workforce</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability to learn and integrate new information</td>
<td>Adopters’ capacity to take in new data and incorporate it with existing knowledge</td>
<td>None identified</td>
<td>Facilitators:</td>
<td>- Support from commissioners to deliver educational activities</td>
<td>- Addressing concerns during educational activities</td>
<td>- Online educational resources</td>
<td>- Identification of training needs</td>
<td>Education and training</td>
</tr>
<tr>
<td>Enablement of knowledge sharing</td>
<td>Creation of venues for sharing information</td>
<td>Local health economy readiness for change: activities supporting innovation (HCPs&amp;KS)</td>
<td>Barriers:</td>
<td>- Lack of integration and co-ordination of educational activities across the health economy</td>
<td>- Educational activities delivered after the launch of new medicine</td>
<td>- No continuous educational support</td>
<td>- Educational activities limited to the target group of clinicians</td>
<td></td>
</tr>
<tr>
<td>Receptive Context for Change</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Leadership and vision</td>
<td>Style of leadership and presence of identified and articulated trajectory with guided direction toward implementation</td>
<td>See Clear goals and priorities</td>
<td></td>
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</tr>
<tr>
<td>Managerial relations</td>
<td>Relationship between staff and programme leadership</td>
<td>None identified</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Risk-taking climate</td>
<td>A work environment that encourages experimentation with new practices, ideas, and technologies</td>
<td>None identified</td>
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</tr>
</tbody>
</table>
| Clear goals and priorities | Explicitness of organisational purposes and aims | Local health economy readiness for change: innovation-health economy fit (HCPs&KS) | Facilitators:  
-New medicine aligns with clinical priorities in the health economy  
-New medicine can be used to deliver those priorities | N/A | Goals and priorities |
| High-quality data capture | Utilisation of context specific data in implementation process | Local health economy readiness for change: activities supporting innovation (HCPs&KS) | Facilitators:  
-Use of medicine information dashboards  
-Use of national and local audit data | N/A | Outcome feedback |
|                      |                                                                                                   | External health system context: national directives (HCPs&KS) | Facilitator:  
-Use practice level data to identify patients eligible for new medicine |                      |
| Tension for change   | Perceived need for change to an organisation’s current provision of services | Local health economy readiness for change: innovation-health economy fit (HCPs&KS) | Facilitators:  
-New medicine(s) seen as an opportunity to improve existing service(s)  
-Reduced delay in receiving therapy with new medicine  
-Deficiencies in existing service performance | N/A | Implications for existing service(s) |
| Innovation-system fit | Compatibility of the innovation with the organisational setting and structure | Limitations of NHS resources; varying local services (P) | Barrier:  
-Local services supporting established medicine use | -Unclear position in clinical pathway | Implications for existing service(s) |
<table>
<thead>
<tr>
<th>Power balances</th>
<th>Relative power of groups invested in implementation (e.g., programme staff, director, management)</th>
<th>Local health economy readiness for change: innovation-health economy fit (HCPs&amp;KS)</th>
<th><strong>Barriers:</strong>&lt;br&gt;- Unclear place in an existing clinical pathway&lt;br&gt;- New medicine might destabilise existing service&lt;br&gt;- Existing service not commissioned to use new medicines (initiate or switch)</th>
<th><strong>Facilitator:</strong>&lt;br&gt;- Existing service(s) support the use of new medicine(s)&lt;br&gt;- No major changes needed to the current clinical pathway(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Value of innovation: affordability (HCPs&amp;KS)</td>
<td><strong>Barrier:</strong>&lt;br&gt;- Existing service for established medicine could not be decommissioned</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment of implications</td>
<td>Estimation of perceived benefits and consequences of implementation</td>
<td>Sociological influences on clinician prescribing: clinician capability (HCPs&amp;KS)</td>
<td><strong>Barrier:</strong>&lt;br&gt;- Disagreement between opinion leaders/clinical leads</td>
<td><strong>Facilitator:</strong>&lt;br&gt;- Joint multidisciplinary work (primary and secondary care)</td>
</tr>
<tr>
<td>Dedicated time and resources</td>
<td>Available means needed to implement an innovation (e.g., funding, time, access,</td>
<td>Limitations of NHS resources: consultation time constraints (P)</td>
<td><strong>Barriers:</strong>&lt;br&gt;- Limited consultation time</td>
<td><strong>Available resources</strong></td>
</tr>
</tbody>
</table>
| Administrative support, etc. | Lack of qualified staff  
- Limited financial budgets of NHS  
Facilitator:  
- Longer consultation times |
|-----------------------------|--------------------------------------------------|
| Local health economy readiness for change: innovation-health economy fit (HCPs&KS) | Barrier:  
- Lack of qualified staff in both established and new service clinics to support its use |
| Sociological influences on clinician prescribing: clinician capability (HCPs&KS) | Barriers:  
- Not sufficient time for consultations in primary care  
- Insufficient level of staffing  
- Additional workload not recognised by commissioners |
| Local health economy readiness for change: collaborative work (HCPs&KS) | Facilitator:  
- GP practices working with independent providers to manage workload |
| External health system context: national directives (HCPs&KS) | Barrier:  
- Lack of or delay in available tools and information to support implementation  
- National recommendations did not consider cost implications for local organisations |
| Monitoring feedback | Providers’ formal and informal opinions on efforts to implement |
| Local health economy readiness for change: activities supporting innovation (HCPs&KS) | Facilitator:  
- Feedback on the level of new medicine use |
| Implementation feedback | N/A |

**Outer Context**

<table>
<thead>
<tr>
<th>Socio-political climate</th>
<th>Social and political factors within the organisation affecting implementation</th>
<th>See Inter-organisational norm-setting and networks</th>
</tr>
</thead>
</table>
| Incentives and mandates | Implicit or explicit inducements, encouragements, or directives to implement | Sociological influences on clinician prescribing: clinician capability (HCPs&KS)  
- Financial incentive from commissioner to use new medicine (low uptake)  
- Limited effect of financial incentives |
| | | N/A |
| Inter-organisational norm-setting and networks | Implicit or explicit rules defining acceptable behaviour; How information is exchanged within the larger organisation | Clinician-patient encounter: varying local services (P) | Barriers: | -Local formulary restrictions to new medicine use  
-Established medicine preference  
-Geographical variation in new medicine availability  

Barriers: | -Value of innovation: affordability (HCPs&KS)  
Barrier: | -Controlled entry of new medicine  

Barriers: | -Local formulary restrictions to new medicine use  
-Established medicine preference  
-Geographical variation in new medicine availability  

Barriers: | -Local health economy readiness for change: promoted prescribing practice (HCPs&KS)  
Barrier: | -New medicine use restricted to certain clinician groups or settings  
-Local guidelines and policies favour existing medicines over new medicine  
-Delay in updating local recommendations in the context of changing local and national practice  
-Unofficial preference of established therapy  

Facilitator: | -Availability of local guideline recommending new medicine  
-No local restrictions for new medicine use  
-Local guidelines updated in line with national recommendations  

Facilitator: | -External health system context: national directives (HCPs&KS)  
Barrier: | -Varying interpretations of national guideline recommendation  

Facilitator: | -National and international guidelines and directives support new medicine use  
-Local guidelines updated to align with national recommendations  

Facilitator: | -Environmental stability | Status of funding and persistence of goals | External health system context: NHS restructuring (HCPs&KS) | Barriers: | -Perceived continuous restructuring of NHS services  
-Changing key contacts within the health economy  

Barriers: | None identified | N/A |
<table>
<thead>
<tr>
<th>Implementation Process</th>
<th>Decision-making</th>
<th>Hands-on approach by leaders</th>
<th>Human resources issues</th>
<th>Internal communication</th>
<th>External communication</th>
<th>Reinvention</th>
<th>Feedback</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation process in selecting a treatment from available options</td>
<td>Direct involvement and oversight of procedure and policy</td>
<td>Adequacy of education and training at all levels of the programme workforce</td>
<td>None identified</td>
<td>None identified</td>
<td>None identified</td>
<td>None identified</td>
<td>None identified</td>
</tr>
<tr>
<td>See Differentiation, Decentralisation, and Power balances</td>
<td>None identified</td>
<td>See Dedicated time and resources</td>
<td></td>
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<tr>
<td>Limitations of NHS resources: consultation time constraints (P)</td>
<td></td>
<td>Limitations of NHS resources: consultation time constraints (P)</td>
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</tr>
<tr>
<td>Barrier:</td>
<td></td>
<td>Barrier:</td>
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</tr>
<tr>
<td>-Challenges understanding information leaflet(s) without explanation from clinician</td>
<td></td>
<td>-Newsletters and bulletins perceived to have low value</td>
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<tr>
<td>Local health economy readiness for change: activities supporting innovation (HCPs&amp;KS)</td>
<td></td>
<td>Local health economy readiness for change: activities supporting innovation (HCPs&amp;KS)</td>
<td></td>
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<tr>
<td>External health system context: national directive (HCPs&amp;KS)</td>
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<td>External health system context: national directive (HCPs&amp;KS)</td>
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<tr>
<td>-Self reported compliance with national guidelines</td>
<td></td>
<td>-Self reported compliance with national guidelines</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Reinvention: Extent to which the innovation can be changed in the process of implementation</td>
<td>None identified</td>
<td>None identified</td>
<td>None identified</td>
<td>None identified</td>
<td>None identified</td>
<td>None identified</td>
<td>None identified</td>
</tr>
<tr>
<td>Feedback: Information exchange between programme staff and external stakeholders</td>
<td></td>
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</tbody>
</table>
Table 7.2 Outcome of research group discussion of the elements of the model initially identified to be excluded.

<table>
<thead>
<tr>
<th>Element of the model</th>
<th>Description</th>
<th>Rationale</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolerance of ambiguity</td>
<td>Adopter’s ability to accept uncertainty</td>
<td>It was agreed that the ambiguity could be reduced by provision of information, education, or training, but these interventions would not change the tolerance of ambiguity. Although tolerance of ambiguity can be changed (increased or decreased), it is a complex process with interventions described elsewhere (Furnham and Marks 2013).</td>
<td>Exclude</td>
</tr>
<tr>
<td>Tenure</td>
<td>Length of employment in setting and in the field. This element was excluded as no factors related to the length of employment were identified in interviews.</td>
<td>The length of employments was not identified in empirical or literature review findings. Although some participants referred to age of clinicians, it is not a modifiable characteristic.</td>
<td>Exclude</td>
</tr>
<tr>
<td>Social Networks</td>
<td>Structure and quality of social network, both formal and informal</td>
<td>Empirical and literature review findings identified that social networks influence the uptake of new medicines. It was discussed that structure and quality of social networks could be changed by creating new social groups or networks, e.g. professional networks for the new medicine or speciality. Also, social networks could be used to increase awareness and knowledge of new medicines.</td>
<td>Include</td>
</tr>
<tr>
<td>Cosmopolitan</td>
<td>Adopter’s strong connections with professional network; Engagement and attendance at professional meetings and other informational venues</td>
<td>It was agreed that this element linked to the “social networks” element of the model. Adopter’s connection with professional network and attendance of professional meetings or events could be encouraged through availability of funding, setting performance targets, role modelling. Thus, it should be considered in the development of components for the toolkit.</td>
<td>Include</td>
</tr>
<tr>
<td>Size/Mature</td>
<td>Number and experience of providers; Date of the programme inception</td>
<td>The findings indicated that certain conditions (e.g. size of the organisation, experience of the workforce) could facilitate the uptake of new medicines. Although the size and maturity of the organisation could be changed through working across organisations and creating integrating systems, these approaches were covered in other elements of the model.</td>
<td>Exclude</td>
</tr>
<tr>
<td>Incentives and mandates</td>
<td>Implicit or explicit inducements, encouragements, or directives to implement</td>
<td>The empirical and literature review findings indicated that financial incentives had a limited impact. It was also agreed that this element of the model was more applicable at national rather than local levels. Furthermore, the intended users of the toolkit will not be in a position to change or create mandates.</td>
<td>Exclude</td>
</tr>
<tr>
<td>Environmental stability</td>
<td>Status of funding and persistence of goals</td>
<td>It was agreed that this element of the model aimed at national rather than local level. Thus, it did not apply to the toolkit focused on local uptake of new medicines.</td>
<td>Exclude</td>
</tr>
<tr>
<td>-------------------------</td>
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<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>External communication</td>
<td>Process by which information is exchanged between providers within the programme and outside stakeholders</td>
<td>It was agreed that the toolkit did not aim to create external reporting. For instance, external reporting as seen with COVID-19 vaccines uptake was not deemed to be appropriate for the uptake of new medicines. The toolkit was aimed to focus on supporting local uptake of new medicines, thus it focuses on internal communication.</td>
<td>Exclude</td>
</tr>
<tr>
<td>Theme</td>
<td>Description</td>
<td>Factors extracted from empirical findings</td>
<td>Factors extracted from literature reviews</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-------------------------------------------</td>
<td>------------------------------------------</td>
</tr>
</tbody>
</table>
| **New medicine cost**             | Cost of the innovation, associated costs, and its cost implications for the healthcare system | Limitations of NHS resources: medicine cost considerations (P) | Barriers:  
  - High cost of new medicine  
  - Lack of consideration of cost-benefits and overall health system costs of new medicines  
  - Wastage in the NHS  

  Value of innovation: affordability (HCPs & KS) | Barriers:  
  - Lack of consideration of cost-benefits and overall health system costs of new medicines  
  - Cost benefits difficult to demonstrate as not available immediately  

  Facilitators:  
  - Consideration of direct health effect costs  
  - Utilising local economical models in decision-making | - High cost of new medicine | Financial impact considerations |
| **Patient factors**               | Patient characteristics and compatibility with patient daily life | Impact on daily life: lifestyle changes (P) | Barrier:  
  - Reduced quality of life  

  Facilitators:  
  - Minimal to no changes required to patient’s lifestyle | - Compatibility with patient’s lifestyle  
  - Patient socio-demographic and clinical characteristics  
  - Patient health status | Patient-centred care |
| **Patient involvement in decision-making** | Patient knowledge about therapy options, involvement in decision-making, and therapy preferences | Clinician-patient encounter: perceived roles (P) | Barrier:  
  - No or limited patient involvement in decision-making  
  - Patients preferring clinician to make decision  
  - Wrong timing of the initial consultation, e.g., acute admission | - No or limited patient involvement in decision-making  
  - Patient feedback and preference | Patient-centred care |
<table>
<thead>
<tr>
<th>Oral anticoagulants</th>
<th>Facilitator:</th>
</tr>
</thead>
</table>
| Knowledge: awareness of therapy options (P) | - Clinician not answering patient’s questions  
  - Patient preferences and circumstances acknowledged |
| Barriers: | - Patient interest and request of new medicine  
  - Patient’s satisfaction with existing therapy |
| Sociological influences on clinician prescribing: patient factors (HCPs & KS) | Facilitator: |
| Barriers: | - No or minimal patient involvement in decision-making  
  - Patients passing decision-making responsibility to clinicians  
  - Patients not informed about new medicines  
  - Patients provided with selective information of available therapy options |
| Barriers: | - Patient preference  
  - Patient enquiries about new medicine  
  - Patients are explained about different therapy options |

P = data from interviews with patients (Chapter 5), HCPs & KS = data from interviews with healthcare professionals and key stakeholders (Chapter 6), NHS = national health service.
7.3.2 Identified components for the future toolkit

During the mapping process, an initial 23 potential components for the future toolkit were identified. After reviewing these components it was clear that some of them were closely related. For instance, “local formulary conditions”, “local and external guidelines”, and “local protocols and guidelines” were concerned with local regulatory policies and clinical guidelines. Therefore, a further refinement of these components was undertaken to prevent components from overlapping with each other (Table 7.4).

<table>
<thead>
<tr>
<th>Initially identified component</th>
<th>Comments</th>
<th>Refined component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Real-life effectiveness</td>
<td>Empirical findings of this thesis suggest that the effectiveness and safety of new medicine are often considered together by clinicians, decision-makers, and patients during the decision-making process.</td>
<td>Effectiveness and Safety</td>
</tr>
<tr>
<td>Safety profile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complexity of use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roles and responsibilities</td>
<td></td>
<td>Implications for existing service(s)</td>
</tr>
<tr>
<td>Implications for existing service(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome feedback</td>
<td>Both initially identified components are concerned with the progress of the uptake of new medicines and their impact on patient health outcomes and service delivery.</td>
<td>Progress update and feedback</td>
</tr>
<tr>
<td>Implementation feedback</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education and training</td>
<td>No change.</td>
<td>Education and training</td>
</tr>
<tr>
<td>Local protocols and guidelines</td>
<td>All three components were concerned with local regulatory policies and clinical guidelines.</td>
<td>Formulary conditions and guidelines</td>
</tr>
<tr>
<td>Local formulary conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local and external guidelines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient-centred care</td>
<td>Care continuity was thought to be part of patient-centred care.</td>
<td>Patient-centred care</td>
</tr>
<tr>
<td>Care continuity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Role of pharmaceutical industry</td>
<td>No change.</td>
<td>Role of pharmaceutical industry</td>
</tr>
<tr>
<td>Opinion leaders</td>
<td>As empirical findings suggested opinion leaders and goals and priorities of both clinician and organisation informed the decision-making.</td>
<td>Decision-making process</td>
</tr>
<tr>
<td>Decision-making process</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goals and priorities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Existing skillset and knowledge of workforce</td>
<td>Both of the components are concerned with available resources to support the uptake of new medicine.</td>
<td>Available resources to support the uptake</td>
</tr>
<tr>
<td>Available resources</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Financial impact considerations</td>
<td>No change.</td>
<td>Financial impact considerations</td>
</tr>
<tr>
<td>Professional and social networks</td>
<td>No change.</td>
<td>Professional and social networks</td>
</tr>
<tr>
<td>Promotion of new medicine</td>
<td>It was felt that promotion of new medicine has already been covered by other components. For instance, marketing by the role of pharmaceutical industry component, raising awareness of new medicine by education and training component.</td>
<td>N/A</td>
</tr>
</tbody>
</table>
It was felt that internal communication has already been covered by other components. For instance, communicating the progress of uptake by progress update and feedback component, communicating preferred therapy options by formulary conditions and guidelines component.

After revising the initial components, a final set of 11 components was developed. These components were:

- Effectiveness and safety
- Financial impact considerations
- Implications for existing service(s)
- Formulary conditions and guidelines
- Available resources to support uptake
- Decision-making process, patient-centred care
- Progress update and feedback
- Education and training
- Role of pharmaceutical industry
- Professional and social networks

It is anticipated that these components could be further refined using a co-design approach with healthcare professionals and key stakeholders in the future. To facilitate further development of these components and formulation of practical and actionable recommendations in future research, discussion points based on empirical points are suggested for each component in Table 7.5.

### 7.4 Summary

This chapter presented how empirical and literature reviews findings were mapped to the Diffusion of Innovations in Service Organisations model by Greenhalgh et al. (2004) to identify potential components of future toolkit development. A total of 11 components were identified that could support the uptake of nationally recommended new medicines within local organisations.

The following and final chapter will present a discussion of thesis findings, strengths and limitations of empirical studies, and outline future research and practice recommendations.
Table 7.5 Proposed components for the future toolkit with suggested discussion point for further development.

<table>
<thead>
<tr>
<th>Proposed construct</th>
<th>Suggested discussion points based on empirical findings</th>
</tr>
</thead>
</table>
| **1. Effectiveness and Safety**         | • Use of latest research evidence to address concerns regarding safety and effectiveness.  
                                             • Addressing concerns of clinicians by utilising local or regional expertise.  
                                             • Collecting and providing local data to clinicians and key stakeholders on effectiveness and safety in clinical practice. |
| **2. Financial impact considerations**  | • Consideration of costs associated with the therapy monitoring, direct health costs, and opportunity costs in addition to medicine unit costs.  
                                             • Monitoring and providing feedback to decision-makers and clinicians on cost outcomes, e.g., savings obtained from direct health costs.  
                                             • Use local economical models in decision-making. |
| **3. Implications for existing service(s)** | • Consideration of positive and negative effects of new medicine impact on existing services.  
                                             • Communication of implications for clinicians.  
                                             • Monitor and provide feedback on service change during the uptake of new medicine (e.g., service evaluation, audit).  
                                             • Consideration of patient feedback on service change. |
| **4. Formulary conditions and guidelines** | • Consideration of restrictions impact on the future use of new medicine - less restrictions, more likely greater use.  
                                             • Aim for a simple clinical pathway to use new medicine with less patient referrals and reduced delay in receiving the therapy.  
                                             • Local guidelines are available with the introduction of new medicine into organisation.  
                                             • Local guidelines are in line with national recommendations, if appropriate.  
                                             • Consider developing cross-sector joint guidelines (for both primary and secondary care).  
                                             • Update formulary status and advice in guidelines as soon as new evidence or national recommendations emerge.  
                                             • Consider ways to increase awareness of new medicine with associated guidelines across the healthcare team concerned. |
| **5. Available resources supporting uptake** | Consideration of resources required to support new medicine use:  
                                             • Clinicians required to implement new medicine.  
                                             • Funding.  
                                             • Additional time of clinicians in consultations with patients.  
                                             • Additional staff to support clinicians implementing new medicine.  
                                             • Addressing current workload needs and additional support needed for new medicine implementation.  
                                             Exploring opportunities to work across organisations, boundaries to share expertise. |
| **6. Decision-making process**          | • Identify roles and responsibilities: who, how, and when should use new medicine.  
                                             • Multidisciplinary approach involving clinicians from primary and secondary care.  
                                             • Aim for a balanced view with representation from “for” and “against” decision-makers. |
| 7. Patient-centred care | • Establish patient clinical needs and impact on daily life.  
|                        | • Establish patient therapy preferences.  
|                        | • Facilitate patient involvement in shared decision-making.  
|                        | • Build a patient-clinician relationship.  
| 8. Progress update and feedback | • Regular monitoring of new medicines use.  
|                       | • Monitor effects of implementation on service and patient outcomes.  
|                        | • Regular feedback to clinicians and decision-makers on the progress.  
|                        | • Communicate changes, updates, and new information within and across different healthcare teams and organisations.  
|                        | • Timely and continuous communication.  
| 9. Education and training | • Establish existing skills and knowledge of the workforce.  
|                      | • Continuous education and training opportunities.  
|                       | • Availability of education and training opportunities offline and online.  
|                       | • Consideration of timing of educational activities.  
|                       | • Integration of education activities across different healthcare groups, departments, and organisations.  
|                       | • Identify local champions to promote and support the use of new medicine.  
| 10. Role of pharmaceutical industry | • Consider utilising resources that could be useful in implementation (printed materials, resources, supporting funding) not available in NHS.  
| 11. Professional and social networks | • Utilising existing or creating new professional networks (for clinicians) or support groups (for patients) and raising awareness and improving knowledge about new medicines.  

Chapter 8 Discussion and Conclusions

8.1 Introduction

This is the first qualitative study informed by implementation theory in the UK exploring the uptake of DOACs across different health economies from the perspectives of patients, healthcare professionals, and key stakeholders. This thesis explored and identified factors affecting the uptake of DOACs for stroke prevention in AF in three health economies in the North of England. Systematic and narrative reviews and two interlinked studies employing a qualitative approach were conducted to achieve the thesis aims. The first study focused on the experiences of patients of consultations when oral anticoagulation therapy was initiated and their views on factors affecting DOAC use. The second study explored the perspectives and experiences of healthcare professionals and identified key stakeholders experiences on DOAC use. This final chapter will discuss how the thesis findings contribute to and broaden current knowledge on the barriers and enablers to the uptake of nationally recommended new medicines for long-term conditions.

Firstly, the overview of the thesis with a summary of the key findings will be presented. It will be followed by a discussion of the findings in the context of other published literature relating to factors influencing the uptake of new medicines and health innovations. Then, the strengths and limitations of the research will be considered. Finally, recommendations for research, practice and policy to optimise the uptake of NICE-recommended new medicines will be outlined.

8.2 Overview of the thesis

Chapter 1 reported that in the UK the relative uptake of nationally recommended new medicines often lagged behind other comparative countries’ health systems, such as Australia, Canada, or France (OLS 2019). Slow adoption of cost-effective health innovations could delay improvements in patient outcomes, healthcare efficiency, and lessen the international competitiveness of the country in the life sciences sector (OLS 2019). One example was the uptake of DOACs used for stroke prevention in AF. The uptake of DOACs was perceived to be slow and to have a high level of unexplained variation across different health economies (ABPI 2016). Consequently, there was a risk of inequality of therapy options offered to patients depending on their place of residence. The first chapter also described the aims and objectives of the thesis.
Chapter 2 presented findings from the systematic review of factors affecting the uptake of new medicines. The identified factors not reported in earlier reviews (Chauhan and Mason 2008; Lubloy 2014; Mason 2008) included patient influence on uptake of new medicines and patient education level, cost of new medicines, formulary and reimbursement restrictions, and guidelines. Patients were reported to influence prescribing decisions through their interest in or request for new medicines, satisfaction with current treatment, and therapy preferences. However, only a small number of studies reported patient influence and they did not explore the impact of patient involvement in decision-making, availability of patient choice, and patient-clinician relationship, which are suggested to influence implementation of health innovations (Chaudoir et al. 2013; Jaakkola et al. 2007; Damschroder et al. 2009). The review findings indicated that the high cost of a new medicine was a barrier but none of the reviewed studies considered the overall costs of new medicines compared to the established therapy (e.g. associated monitoring cost) or health economics (e.g. direct health costs). The review findings also reaffirmed that prescribers’ experience and knowledge, peer influence, pharmaceutical detailing, staff composition at organisations, and scientific literature influence uptake of new medicines. Moreover, the reviewed studies were deficient in not using determinant frameworks or implementation theories to address wider patient, prescriber, and organisational factors in understanding barriers and facilitators to the uptake of new medicines into clinical practice. Also, most studies reviewed were quantitative, used secondary data from various databases, e.g. insurance databases, and were of medium or high quality. Lastly, the reviewed studies reported perspectives of clinicians and decision-makers with no or limited insight into patients’ views. The systematic review findings contributed to the decision to employ a qualitative approach to collect empirical data described in this thesis.

Chapter 3 reported the narrative review findings aiming to explore the patient role in the uptake of DOACs through their involvement in decision-making. The findings revealed that influence of patients, or lack of it, on the decision to prescribe oral anticoagulants was linked to their involvement in the decision-making process, which ranged from a limited to an autonomous role. Patients tended to be provided with selective information, which was influenced by prescribers' views, to steer them towards the prescribers' preferred therapy option. However, inclusion of studies when
warfarin with at least one DOAC were available as therapy options highlighted the emergence of patient involvement in the decision-making process from both patient’s and prescriber’s perspectives. Barriers reported for patient involvement included limited time in consultations, acute hospital admission, patients’ lack of knowledge about therapy options, and patients viewing it was the clinician's role to make decisions. The narrative review findings contributed to the decision to interview patients as well as healthcare professionals and key stakeholders during the data collection.

Chapter 4 described the methodology guiding the research into factors affecting the uptake of new medicines from the perspectives of patients, prescribers, and key stakeholders. The study adopted a qualitative research approach underpinned by a critical realism philosophical framework. The Diffusion of Innovations in Service Organisations model by Greenhalgh et al. (2004) was selected as a conceptual framework to guide the research. Theoretical sampling was used to recruit participants from primary and secondary care. Data were collected using semi-structured interviews and analysed using the Framework method.

Chapter 5 provided an in depth analysis of patients’ views on the barriers and enablers to the uptake of DOACs for stroke prevention in AF. The 21 patient participants interviewed recalled their experiences of consultations when oral anticoagulants were started, their involvement in decision-making, therapy choices offered, and their experience with the prescribed oral anticoagulant therapy. While there were a wide range of experiences and views, altogether patient narratives reveal a number of factors influencing what therapy options were presented and prescribed to patients and consequently influencing patients’ satisfaction with the prescribed therapy. The findings indicated that barriers to DOAC use were often linked to a lack of patient involvement in decision-making. Patients also reported a lack of time to discuss therapy options, no routine reviews of existing prescribed therapy, prescribers’ preferences, high cost of DOACs and NHS resource limitations (financial and workforce), patient and prescriber lack of knowledge of therapy options, and safety concerns with DOACs as perceived barriers for DOAC use. Reported barriers to DOAC use led to some patients receiving warfarin therapy, which did not align with the needs of their daily lives. Some patients reported it caused undue stress and non-adherence.
Chapter 6 provided an in depth analysis of healthcare professionals' and key stakeholders' views on the barriers and enablers to the uptake of DOACs for stroke prevention in AF. They recalled the process and their experiences of DOACs being introduced in their practice, organisation, and the health economy. Forty-six interviewed participants discussed how the anticoagulation practice and services changed with the introduction of DOACs and reflected on the barriers and enablers they experienced to their use. Participants' perception of the value of the innovation (real-life effectiveness, safety, affordability, practical convenience) was observed to influence their decisions to support or oppose the local implementation of DOACs. Furthermore, peer influence, patient demand, and patient preferences were identified as factors. The findings also revealed that health economy readiness for change (DOACs alignment with local clinical priorities, local guidelines, formularies, and resources) and external health system context (national directives and guidelines, NHS restructuring, and pharmaceutical industry) influenced the uptake of DOACs. The interview also highlighted strategies used to improve or restrict the uptake of DOACs and tensions between providing patient-centred care and managing financial implications for commissioners.

Chapter 7 presented how the findings from the interviews and conducted literature reviews were used to identify potential components of a future toolkit for use in clinical practice to address the identified barriers to the uptake of new medicines. A total of 11 components were proposed for further development and inclusion in the future toolkit.

8.3 Discussion of key findings

The findings from literature reviews and interviews with patients, healthcare professionals, and key stakeholders identified multiple intersecting factors acting as barriers or enablers to the uptake of DOACs. Notably, there was an agreement between the views of patients and healthcare professionals/key stakeholders on several identified factors (Figure 8.1). Both groups perceived the cost, safety, efficacy, and practical convenience of DOACs having an impact on the use of DOACs. Also, both groups described the experience, knowledge, and therapy preferences of prescribers as well as patient involvement in decision-making influencing the uptake. While interviews with healthcare professionals and key stakeholders highlighted factors linked to local health economy readiness for change (e.g. DOAC and health-economy fit) and the external health system context (e.g. national directives), patients
referred to limitations of NHS resources. The following sections will discuss these findings in the context of existing literature, theory, and policy in the UK.
Figure 8.1 Summary presentation of factors identified by patients, healthcare professionals and key stakeholder, and by both participant groups.
8.4 Real-world evidence on new medicines

The efficacy and safety of DOACs for stroke prevention in AF has been demonstrated in landmark clinical trials: dabigatran in RE-LY (Connolly et al. 2009), rivaroxaban in ROCKET AF (Patel et al. 2011), apixaban in ARISTOTLE (Lopes et al. 2010), and edoxaban in ENGAGE AF-TIMI (Giugliano et al. 2013). It was further confirmed by a network meta-analysis of 23 randomised clinical trials (López-López et al. 2017). Despite clinical evidence available confirming the efficacy and safety of DOACs, both patients and staff discussed perceived efficacy and safety impact on the uptake of DOACs and lack of real-world evidence (i.e. evidence obtained from use in clinical practice) to provide assurance.

8.4.1 Effectiveness

The interview findings have highlighted the importance of real-world evidence on the uptake of new medicines, which was not reported in the systematic (Chapter 3) and previous (Chauhan and Mason 2008; Mason 2008; Lubloy 2014) reviews. The findings also suggested that the effectiveness was considered more by healthcare staff than patients.

Patient narratives suggested that they did not question the effectiveness of DOAC or warfarin therapies. They perceived them to be effective, and thus effectiveness had minimal or no influence on patients' choice of oral anticoagulant. Clinicians and key stakeholders, however, compared the efficacy of DOACs to the existing therapy, i.e., warfarin. This aligned with the findings of this thesis that perception of the effectiveness of new medicines influences their uptake. The study findings also demonstrated that perception of the effectiveness of DOACs varied between participants. Clinicians, prescribing DOACs for their patients, discussed that they were more effective in patients with inadequate warfarin control, provided immediate risk reduction of AF-related stroke, and were more stable and reliable due to fewer interactions (e.g. food, medicines) than warfarin. Contrastingly, clinicians preferring warfarin had a more cautious approach to DOAC use due to limited real-world evidence to assure the efficacy demonstrated in clinical trials translated into clinical practice. These clinicians expressed concerns that patients without frequent monitoring and outside the controlled clinical trial environment could be more non-adherent than patients on warfarin therapy. Concerns about poor compliance with
DOAC therapy, resulting in increased AF-related stroke risk, have been reported in
the literature (Burn and Pirmohamed 2019; Rodriguez et al. 2013; Salmasi et al. 2020).
However, adherence issues are not unique to DOACs, as it is estimated that up to
nearly half of patients are non-adherent to their long-term treatments (Kripalani et al.
2007; WHO 2003). Despite frequent monitoring associated with warfarin therapy, poor
compliance (Kimmel et al. 2007) and under anticoagulation (Pokorney et al. 2015)
have been reported. A systematic review of 37 trials concluded that dose regimen
simplification was the most successful intervention in improving adherence. Other
interventions thought likely to be successful were educational counselling, self-
management plans, reinforcement, monitoring and feedback delivered over multiple
sessions (Kripalani et al. 2007). However, another systematic review concluded that
there was a lack of evidence-based interventions to improve adherence (Williams et
al. 2008). Bartoli-Abdou et al. (2018) demonstrated that illness beliefs, medicine
beliefs, and quality of life were linked with warfarin adherence. Thus, addressing
patients' illness and medicines beliefs, improving their knowledge about the illness,
involving patients in self-management, and reducing the burden of therapy could
support medicine adherence (Abdou et al. 2016; Bartoli-Abdou et al. 2018)
The narratives of clinicians and key stakeholders implicitly suggested that increasing
availability of real-world evidence demonstrating the efficacy and safety of DOACs
was one of the facilitators for the increased use of DOACs. As time went on, more
real-world evidence became available. For instance, a systematic review and meta-
analysis of 28 real-world studies confirmed findings from the landmark clinical trials of
DOACs and was published five years after the first DOAC was licensed (Ntaios et al.
2017). Real-world evidence is not available at the time of the launch of new medicines.
As expected, studies using large administrative datasets are published at least several
years later. Thus, concerns of clinicians regarding the effectiveness and safety are not
addressed quickly. These concerns could be addressed more promptly with the
collection of local data to evaluate new medicines' efficacy and safety.
Some participants in the study described collecting local data on AF-related stroke
prevention associated with DOACs use and sharing with local clinicians and decision-
makers. They commented that the observed positive impact on patient health
outcomes encouraged decision-makers and some clinicians to move from warfarin to
new therapies. The real-world evidence has already been used in regulatory decisions
in the USA (FDA 2018). Its value has been recognised by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK. The MHRA has recently announced the start of the Innovative Licensing and Access Pathway (MHRA 2021). This pathway, aimed at innovative medicines meeting pre-defined criteria, will use continuous benefit-risk assessment integrating real-world evidence alongside other tools to accelerate patient access to innovative medicines. The pathway has a potential to increase the use of real-world evidence in evaluating products and developing guidelines in the UK, increasing the confidence of clinicians, key stakeholders, and patients in the efficacy and safety of newly marketed medicines from the start.

8.4.2 Safety profile

The findings from interviews in this thesis reinforce the importance of the safety profile of new medicines in therapy decisions and thus their uptake as demonstrated in the systematic review in Chapter 2. Both patients and healthcare professionals discussed concerns regarding unknown adverse and long-term effects of DOACs. Familiarity with warfarin provided confidence to participants, whereas uncertainty with DOACs caused concern about the unknown risk. Past cases of new medicines being withdrawn in the post-marketing stage due to safety risks, e.g. rofecoxib and sibutramine due to an increased risk of cardiovascular events (Graham et al. 2005; James et al. 2010), also added to the general anxiety about using new medicines.

Some clinicians and stakeholders were worried about the unknown bleeding risk with DOACs in clinical practice and a lack of reversal agent, despite clinical trials (Connolly et al. 2009; Giugliano et al. 2013; Lopes et al. 2010; Patel et al. 2011) demonstrating a safer bleeding profile compared to warfarin. The lack of a reversal agent was suggested to be a barrier to the uptake of DOACs by this thesis findings. There are currently no studies exploring the change in the uptake of DOACs since the availability of reversal agents (Chaudhary et al. 2020). The message of lack of reversal agents from stakeholders and clinicians raised concerns for some prescribers, particularly for clinicians with limited experience in managing bleeds. Some participants described the strategies used to overcome concerns about bleeding risk with DOACs. These strategies included monitoring the local incidence of bleeds for patients on DOAC therapy, providing education to less experienced clinicians, having experts addressing clinicians’ concerns in educational events, and developing local protocols for reversing
DOACs. The importance of the reversal agent varied between clinician and stakeholders. Some were of the view that due to pharmacological attributes (short half-life) of DOACs, the reversal agent had limited value and to others, the lack of the reversal agent limited DOAC use.

Nevertheless, some participants suggested that the concerns about bleeding risks and the need for a reversal agent diminished over time with, more data available confirming safety (López-López et al. 2017). However, a recent longitudinal study of over 5,500 GP practices in the UK suggested that an increase in DOAC use could be linked to the higher rate of emergency bleeding admissions (Alfirevic et al. 2020). Although the use of DOACs is currently widespread, new evidence raising concerns about their safety could and should affect their continuous use to ensure no harm is caused by prescribed therapies. Similar to addressing efficacy concerns, local data on adverse effects with new medicines could be collected and shared with clinicians and commissioners to inform decision-making.

8.5 Financial impact of new medicines

The importance of the financial impact of new medicines to health economies was evident in this study exploring the uptake of DOACs. This thesis findings indicate that cost of new medicines influences their uptake. Importantly, the findings from interviews in this thesis further add to the body of knowledge on cost impact by indicating that not only the selling price but also wider economic costs (e.g. direct health outcome, opportunity, and societal costs) are considered during decision-making. Also, the findings of this thesis indicated that costs (total or not) influenced decisions on local DOAC availability through formulary conditions and local guideline recommendations.

8.5.1 New medicine selling price

Although the selling price of a new medicine is not considered during marketing authorisation (also known as product licence) decisions (EMEA 2020), it is pivotal in determining if the medicine is cost-effective (NICE 2021). NICE evaluates new medicines by considering their clinical and economic evidence and produces recommendations based on the evaluation, i.e., NICE technology appraisal (NICE 2021). NICE-recommended medicines are made available within the NHS. Even though DOACs were deemed cost-effective and recommended by NICE, both patients and healthcare professionals, in line with the systematic review findings (Chapter 3),
suggested that the high cost of DOACs compared to warfarin was a barrier to their uptake in the "cash-strapped NHS". Some patients knew that the price of a DOAC was higher than warfarin, and they were of the opinion that prescribers favoured warfarin due to the lower cost. They believed it was one of the reasons why they were not told about DOACs in consultations. Previous studies about DOACs showed that prescribers in countries where patients were charged for medicines through insurance were less likely to prescribe DOACs, especially for patients with lower income levels (AbuDagga et al. 2014; Baik et al. 2016; Huang et al. 2013; Kirley et al. 2016; Patel et al. 2015; Salmasi et al. 2020). However, no such studies in countries with national health services such as the UK have yet been reported. DOACs are nearing the end of their patents by 2023, hence the price of DOACs are anticipated to fall with the introduction of the first generic versions. The anticipated reduction in price for generic DOACs could further increase their uptake.

It was suggested that some local recommendations were based on the unit cost of DOACs. For instance, Burn and Pirmohamed (2018) argue that DOACs should be used in certain groups of patients (e.g. working age, unable to take warfarin) to make them of better value to the healthcare system. However, in such scenarios, patient-centred care that acknowledges patient preferences would not be delivered. A possible way to deliver patient-centred care and consider the cost of therapy would be to have cost conversations between patients and clinicians (discussing costs of healthcare with patients). However, available evidence on cost conversations in healthcare is mainly limited to studies conducted in the USA where patients need to pay for healthcare services (Harrington et al. 2020). It could be argued that the usefulness of such conversations would be of less value in the UK as the healthcare service is free at the point of care and patients who pay for NHS prescriptions pay a set fee rather than the price of the medicine. Also, similar to a previous study (Schafheutle 2008), patients in this study had different views on the cost of medicines. Some patients were not concerned about taking a cheaper medicine, others viewed that the cost of medicine should not be a factor in decision-making since they already pay towards the NHS. Nevertheless, studies conducted with patients non-exempt from prescription charges reported that the cost of a prescription was an issue for some leading to non-adherence (Atella et al. 2012; Schafheutle et al. 2002). Notably, these patients did not inform their GPs about affordability concerns and awareness of support to reduce...
prescription costs (e.g. pre-payment certificates) was low amongst participants. Hence, cost conversations could identify and address affordability issues to improve adherence, but future research is needed to explore its value in the UK context.

8.5.2 Associated monitoring costs

Some patients and healthcare professional also considered associated monitoring costs of therapy. As DOACs do not require frequent monitoring like warfarin, some participants viewed DOACs as similarly expensive or even cheaper for patients requiring very frequent warfarin monitoring. The cost of warfarin monitoring is difficult to determine as there is no national tariff and cost are negotiated between local commissioners and providers. Therefore, the cost of a monitoring service can vary between settings and health economies. The cost could also depend on the frequency of monitoring necessary. For instance, patients with inadequate international normalised ratio (INR) control would need more frequent appointments, e.g. weekly, whereas patients with good INR control could be seen every 12 weeks. Consequently, it is difficult to precisely quantify the warfarin monitoring costs (NICE 2014c). This could explain why some participants stated that these costs are not readily available to clinicians or even decision-makers to inform local decision-making. The estimated annual prescription cost for DOAC therapy is £600 to £800 per patient (Burn and Pirmohamed 2018). The estimated mean warfarin prescription with associated monitoring costs used by NICE in 2012 was around £250 per patient per annum (NICE 2014c) and increased to around £280 (£141 in secondary care, £424 in primary care) in 2020 (NICE 2020b). However, these estimates are acknowledged to have a high degree of uncertainty due to the earlier stated reasons. The annual monitoring cost could be lower for patients with good INR control. It could explain why some clinicians in this study preferred to continue warfarin or not inform such patients about the possibility of switching to DOAC therapy and local policies reserved DOACs for patients with inadequate warfarin control. Also, the higher cost for local warfarin monitoring service would make DOACs comparatively less expensive and enable their uptake, which was described in health economy A. Contrastingly, in health economy B the warfarin service was described as a relatively low cost and DOACs were initially provided through a specifically designed anticoagulation clinic in secondary care. Thus, the cost of DOAC therapy was further increased and it became a less attractive option, which potentially contributed to the observed low uptake.
Some participants also noted that monitoring for DOACs was performed in clinical practice (e.g. renal and liver function checks) potentially increasing their costs further. National guidance recommends regular follow up every three months and annual monitoring of renal and liver function tests, and the full blood count (NICE 2020c). This monitoring was not included in the NICE cost-effectiveness analysis but some participants in this study viewed it to be part of the patient’s annual review, which is not costed in other medicines costs either.

8.5.3 Cost-effectiveness

Although patients did not refer to direct health outcomes costs, some clinicians and decision-makers discussed savings from stroke prevention and additional costs from potential bleeding complications. They viewed stroke as an expensive negative health outcome causing a detrimental effect on patients and needing high care costs. The cost-effectiveness model used by NICE estimated the mean cost of stroke event to be approximately £14,000 and the mean post-ischaemic stroke care to cost almost £17,000 per patient per annum (Sterne et al. 2017). Some healthcare professionals in this study stated that the considerably higher costs of stroke justified the use of DOACs. A few clinicians, concerned with the unknown bleeding risk associated with DOACs in clinical practice at the time, stated that reversal agents for DOACs were considerably more expensive than vitamin K used for warfarin. In their view, the potential cost of DOACs was further increased, contributing to their reluctance in using them. However, the utilisation of DOAC specific antidotes in the UK has not been reported. Some participants viewed their use to be limited in clinical practice and thus having an insignificant effect on DOACs cost.

Many cost-effectiveness studies concluded DOACs to be cost-effective therapies (Coyle et al. 2013; Harrington et al. 2013; Lip et al. 2014; López-López et al. 2017; Sterne 2017; Zheng et al. 2014). Some of these studies indicated that the total mean costs were lower for warfarin (Coyle et al. 2013; Harrington et al. 2013). However, several cost-effectiveness analysis studies estimated apixaban (5mg twice a day) or dabigatran (150mg BD) to be the most cost-effective anticoagulation therapies (López-López et al. 2017; Sterne 2017; Zheng et al. 2014). Warfarin was suggested to be not the most cost-effective therapy (Sterne et al. 2017; Zheng et al. 2014). However, the authors note a high degree of uncertainty around the costs for all treatments (Sterne et al. 2017). It was suggested that the estimated better cost-effectiveness profile of
some DOACs was due to their improved efficacy and reduced bleeding risk of apixaban compared to warfarin (López-López et al. 2017; Sterne 2017).

The health economic analysis by Sterne et al. (2017) was used to inform the update of the NICE AF management guideline. The proposed changes to the guidelines recommend apixaban and dabigatran (both twice a day dosing) as first-line oral anticoagulants for stroke prevention in AF and warfarin for patients unable to take DOACs. The research in this thesis indicated that national guideline recommendations influence local decisions regarding new medicine use and the uptake of new medicines. The changes promoting the use of DOACs in the updated NICE AF management guideline (NICE 2020b) will likely increase the uptake of DOACs further.

A few participants discussed “opportunity costs” (described as “benefits forgone by particular use of resources” (Palmer and Raftery 1999, p.1552)). In their view, warfarin was a better value medicine considering cost, efficacy and safety for the NHS and the high costs of DOACs meant that increasing expenditure on DOACs displaced funding for other healthcare services, e.g. mental health, social care. Also, the observation indicated that some participants considered the financial impact of new medicines on the whole local population. Although a significant expenditure on anticoagulants is reported with the introduction and increasing use of DOACs (Burn and Pirmohamed 2018; Orlowski et al. 2021), the AF-related stroke incidence fell and overall, per-patient costs reduced, resulting in net savings for the NHS (Orlowski et al. 2021). However, evidence of new medicine opportunity costs and impact on health budgets is not readily available, in particular in the first years after a new medicine launch.

8.5.4 Indirect societal costs

A few patients and clinicians discussed the societal costs of warfarin that were informing their perception of total costs of DOACs compared to warfarin. The discussed costs included employment time and leisure time lost by attending warfarin monitoring, and the cost of the travel to the warfarin clinic. These identified indirect costs linked with warfarin portrayed DOAC therapy as a more advantageous option for a few participants. Studies outside the UK looking at societal costs associated with warfarin monitoring estimated the average cost to be between 13 and 49 EUR for the patient per clinic visit (Briere et al. 2017; Jowett et al. 2008; Leminen et al. 2019; Marcolino et al. 2016; Walsh et al. 2014). Only one UK study was identified to consider
warfarin monitoring costs for patients. The estimated time cost for a patient being off work was £1.20 per visit, however, the study population comprised of patients >62 years (Ali et al. 2012). Although it is debatable if consideration of societal costs is within the scope of the healthcare service, they can influence the decision-making of patients and clinicians.

8.5.5 Management of local health budgets

NHS commissioners within local health economies have a legal obligation to resource and fund NICE-recommended new medicines, deemed to be cost-effective during the technology appraisal process, within three months of the published decision (NICE 2021). The thresholds employed by NICE for assessments are not directly related to the NHS budget nor does it consider the impact on local health economies’ health budgets (Schaffer et al. 2016). Thus, tensions between funding cost-increasing new medicines, i.e., DOACs, and managing fixed local health budgets have been described in this study. This thesis findings’ revealed that the interpretation of total costs of new medicines varied between health economies and decision-makers, which could be explained by a previous study suggesting that there is a lack of resources to produce and understand the cost-effectiveness evidence at the local health economy level (Robinson et al. 2012). A few participants commented that NICE-provided tools for costing impact of DOACs on local resources (NICE 2014b) which was time-consuming and complex. Contrastingly, decision-makers in health economy C had the support to produce local modelling indicating what level of DOAC use of all oral anticoagulants was cost-effective or cost-neutral for the local population and informed the commissioning decisions. However, a few participants commented that the understanding of total costs or clinical pathway costs of new medicine improved over time, indicating more support in producing and interpreting local cost-effectiveness data is required.

Furthermore, research findings in this thesis demonstrated how local decision-making was also hindered by the compartmentalisation of local commissioning. Some commissioners described how funding for new medicines and associated monitoring came from separate budgets. Also, savings or expenditure due to health outcomes (stroke, bleeding) linked to new medicines were absorbed by a budget other than the budget that funded the medicine. Hence, these savings were not visible to clinicians or decision-makers, potentially limiting the use of DOACs. Availability of such
information or sharing the savings between the clinician department and commissioners could promote the use of cost-effective medicine (Aladul et al. 2018). As the budgets were not linked, in some health economies total local costs of warfarin or potential costs of DOACs were not available nor considered during local decision-making. The observed complexities of local commissioning have also been recognised in a study by Checkland et al. (2018). Moreover, Checkland et al. (2018) observed that local health economies were under pressure to maintain financial balance. It could explain why some commissioners in this study preferred warfarin, which had a lesser financial impact on their medicine budgets. Also, in line with a previous study, commissioners were observed to be more cost-cautious than clinicians (Prosser and Walley 2005). Clinicians prioritised the needs of patients in prescribing decisions (Chapman et al. 2017; Prosser and Walley 2005).

8.6 Patient role in the uptake of new medicines

Over the years, patient-centred care and patient involvement in healthcare decision making have become an indicator of good quality healthcare (Department of Health 2015; Loughlin et al. 2019). Consequently, prescribing decisions are shaped not only by demographic and clinical characteristics of patients but also increasingly by what is important to patients (Bomhof-Roordink et al. 2019). However, patient influence on the uptake of new medicines has scarcely been reported in the literature as the systematic review findings in Chapter 2 indicate. Importantly, the findings from the interviews in this thesis provide considerable insight into patient influence on the uptake of new medicines, thus expanding the understanding of the patient role in the uptake of new medicines. Patient influence was enacted through patient demand for new medicines and participation in therapy decision-making.

8.6.1 Patient involvement in decision-making

Shared decision-making (SDM) between clinicians and patients has increasingly been adopted as a model to deliver patient-centred care when making healthcare decisions. A review by Bomhof-Roordink et al. (2019) identified 40 SDM models developed for use in healthcare. Half of the models were published in the last five years, indicating increasing SDM importance in current healthcare. Although the interpretation of SDM varies between clinicians and there is no consensus on how best to achieve it in
practice (Bomhof-Roordink et al. 2019; Elwyn 2020; Gravel et al. 2006), the identified most frequent components of SDM are presented in Table 8.1.

**Table 8.1 The most frequently included components in SDM models (adapted from Bomhof-Roordink et al. (2019)).**

<table>
<thead>
<tr>
<th>Component</th>
<th>Description of the component</th>
</tr>
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<tbody>
<tr>
<td>Describe treatment</td>
<td>Clinician informs the patient of available options and presents evidence by describing the benefits, risks and feasibility of those options.</td>
</tr>
<tr>
<td>options</td>
<td></td>
</tr>
<tr>
<td>Patient preferences</td>
<td>Clinician establishes the patient's concerns, goals of care, preferences, and values to inform decision-making.</td>
</tr>
<tr>
<td>Make the decision</td>
<td>The discussion about the decision is documented and a decision is made or explicitly deferred for a later time. The decision is also revisited at a later date. The patient retains ultimate authority over the decision.</td>
</tr>
<tr>
<td>Tailor information</td>
<td>The clinician uses clear language, ascertains the preferred format for information, and checks and clarifies, if needed, the patient's understanding.</td>
</tr>
<tr>
<td>Deliberate</td>
<td>The clinician uses deliberation or negotiation in case of disagreement with the patient regarding the decision made.</td>
</tr>
<tr>
<td>Create choice</td>
<td>Clinician explicitly states the need for treatment and recognises that the patient's situation may change and there is more than one decision that could address the change in the situation.</td>
</tr>
<tr>
<td>awareness</td>
<td></td>
</tr>
<tr>
<td>Learn about the</td>
<td>Clinician checks and clarifies their understanding of the patient and learns about the patient to ensure the treatment aligns with the patient's needs and circumstances.</td>
</tr>
<tr>
<td>patient</td>
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The component “describes treatment options” aims to equip patients with knowledge about available treatment options and thus enable them to participate in decision-making. It would include informing patients about existing and new medicines applicable to their clinical situation. The study findings in Chapter 5, in line with prior survey research (Choi et al. 2014; Nowell et al. 2017; Pritchett et al. 2020), indicate patients experiencing joint or autonomous decision-making have been told about more than one therapy option. Whereas patients, mostly prescribed warfarin, presented with only one treatment option and not informed about DOACs reported no or limited involvement in decision-making. The presence of a lack of treatment options presented to patients with no or limited involvement in decision-making has also been observed in the narrative review findings (Chapter 4). Gaps in patients' knowledge about treatment options have been suggested to be a barrier to achieving SDM (Nijhuis et al. 2019; Silva et al. 2012). It could explain why narratives of some patients in Chapter 5 reported a lack of self-confidence, which prevented them from participating in decision-making. The study findings in Chapter 6, in agreement with the narrative review (Chapter 4), observed that some clinicians provided selective or biased information to patients, which was based on their preferences and beliefs, e.g.
one therapy option, downplayed the bleeding risk of DOACs. Incomplete information hindered patient involvement in decision-making.

The “tailor information” component links with the “describes treatment options” as information provided needs to be in the format the patient prefers (e.g. written, verbal) and language the patient understands (e.g. lay language without jargon). It is also suggested that clinicians check patient understanding and provide further clarification when needed. However, describing and providing information on treatment options does not guarantee patient involvement in SDM (Bomhof-Roodink et al. 2019; Silva et al. 2012). The findings in Chapter 5 and 6 indicate that not all patients want to be involved in decision-making. Unwillingness to be part of decision-making could be due to lack of knowledge about therapy options, perceiving it was the clinician’s role to make decisions or did not think they could be involved due to historical ways of consulting. Consequently, the chosen decision was perceived to be informed by clinicians’ preferences. These observations were in agreement with the narrative review (Chapter 4) and earlier review (Borg et al. 2012) findings. Regardless of the patient's willingness to participate, the patient's preferences need to be established to achieve a decision that is in the patient's best interest.

“Patient preferences” is another important aspect of SDM (Bomhof-Roodink et al. 2019; Department of Health 2015; Loughlin et al. 2019; Silva et al. 2012). The results in Chapter 5 and 6 indicate patients who had an opportunity to voice their preferences, shaped by their knowledge about oral anticoagulants gained from their clinicians or social network, influenced which medicine was prescribed (i.e. warfarin or DOAC). Also, “patient preferences” are closely linked with the “learn about the patient” component. Clinicians need to learn about their patients to align the therapy with their routines and lifestyle. The interview findings presented in Chapters 5 and 6 indicate patients, when given an opportunity, consider the impact of presented therapy options on their daily lives and prefer a medicine causing lesser interference to their daily lives and with a simpler dosing regimen. Narratives from prescribers also suggested that impact on patient lives and patients’ preferences were considered in decision-making to achieve better compliance with the prescribed therapy. These results align with those of previous studies reporting patients’ preference for medicines with simpler dosing regimens and less disruption to their routines (Ingersoll and Cohen 2008; Srivastava et al. 2013). The findings in Chapter 5 also suggested that the lack of
therapy options presented, the lack of opportunity for patients to voice their preferences, and consideration of therapy impact on their daily lives resulted in some patients having negative experiences with the prescribed therapy, mostly warfarin. Some patients described experiencing challenges with attending required monitoring and taking correct doses of warfarin or even reported it causing undue stress and non-adherence. These results further support the idea that acknowledging patient preferences and needs could potentially achieve better therapy adherence, patient satisfaction with the consultation and therapy, and overall health (Ingersoll and Cohen 2008; Shay and Lafata 2015; Srivastava et al. 2013). Thus, prescribed therapy should be tailored to patients' needs and preferences to ensure the therapy fits with their daily lives.

Patients should also be provided with an opportunity to make the decision, if clinically appropriate, at a later time or have the made decisions revisited and reviewed as indicated by the “make the decision” component. A few patients in the study decided to make the therapy decision once they gathered enough information for an informed decision. Other patients prescribed warfarin described how the therapy decisions were not reviewed or discussed when alternative medicines, i.e. DOACs, became available. Some of these patients learnt about DOACs from their social networks and asked their clinicians about switching to therapy with the new medicine. Only patients observed to be non-adherent to warfarin therapy or monitoring, or experiencing adverse effects, had their therapy reviewed. Moreover, some patients stated participation in decision-making during acute hospital admission when feeling unwell was not the right time for them. Revisiting the chosen decision after the hospital admission can give the opportunity for such patients to be involved in decision-making. Therefore, to ensure patient preferences are acknowledged, periodic review of patients' satisfaction with their current prescribed therapy and the option to consider alternative therapy options, which potentially could identify and resolve difficulties patients experience that clinicians might not be aware of, should be implemented in patient care.

Although SDM is promoted within healthcare services, delivery of it in clinical practice remains a challenge (Borg et al 2012; Gravel et al. 2006). The main barriers for patient involvement identified in this thesis included patient and clinician perceptions of roles in consultations, patients’ lack of knowledge needed for decision-making, and clinician’s view of patient involvement in decision-making. Furthermore, lack of
relationship with a clinician, limited time in consultations, and acute hospital admission were suggested to hinder patient involvement in decision-making. These factors were consistent with the narrative review (Chapter 4) and previous reviews’ (Borg et al. 2012; Gravel et al. 2006) findings. Other reported barriers in literature were clinicians’ lack of knowledge of SDM, lack of agreement with specific components of SDM models (e.g. asking a patient about their values) or in general (e.g. not practical, not cost-beneficial, not applicable), and limited resources or incentives to deliver SDM (Gravel et al. 2006; Silva et al. 2012). Some of these barriers can be overcome by providing training to both patients and clinicians about SDM, use of decision aids, and achieving organisational culture and infrastructure supporting SDM (e.g. leadership support, patient-centred culture) (Silva et al. 2012). In some clinical conditions, like anticoagulation in AF, developing and dedicating a team of healthcare professionals with expertise in the new medicine and health condition they are indicated for, to initiate the treatment would facilitate SDM and provide continuity of ongoing care to build rapport with a patient. Lastly, as patient involvement in decision-making will likely be increased in the future, more studies are needed to confirm the findings of this thesis and influence of patients on the use of new medicines.

8.7 Experience of clinicians and peer influence

The findings of this thesis are consistent with previous reviews (Chauhan and Mason 2008; Mason 2008; Lubloy 2014) that knowledge and experience of clinicians and their professional networks influence the uptake of new medicines, i.e. DOACs.

8.7.1 Knowledge and experience

As suggested by this thesis, the knowledge and experience of the local clinicians could in part explain why the uptake of DOACs differed between the studied health economies. Conforming to previous studies, clinicians’ lack of experience or knowledge of anticoagulation, DOAC use or both, was a barrier to the uptake of DOACs (Anderson et al. 2018; AbuDagga et al. 2014; Brais et al. 2017; Huang et al. 2013; Patel et al. 2015; Potpara et al. 2017; Zhang et al. 2019). There were notable differences in willingness amongst primary care clinicians across the studied health economies to use DOACs, which was related to their knowledge and experience. In one of the studied health economies, primary care was perceived to drive the use of DOACs as primary care clinicians were experienced in prescribing and managing
warfarin and also using one of the DOACs for a different clinical condition. This observation corroborates with our earlier quantitative study in the same health economy showing that the majority of new oral anticoagulant prescriptions, warfarin or DOAC, were initiated by GPs (Medlinskiene et al. 2019). Whereas in another health economy, primary care clinicians lacked experience in managing oral anticoagulants and thus were less willing to start using DOACs. As such, secondary care clinicians were mostly responsible for the early uptake of DOACs, which is consistent with national DOAC utilisation studies in Canada (Weitz et al. 2015), Denmark (Pottegard et al. 2014), and USA (O’Neal et al. 2018) reporting earlier uptake of DOACs between secondary care rather than primary care clinicians. The findings from interviews also highlight that the choice of DOAC was influenced by clinicians experience with and knowledge of the medicine.

8.7.2 Peer influence

The findings of this thesis indicate that peer influence within or outside the organisation influences the uptake of new medicines. Secondary care clinicians, as in previous research (Lin S et al. 2011; Karampli et al. 2020; Murphy et al. 2018; Tobin et al. 2008), were suggested to influence prescribing decisions of primary care clinicians and thus the use of DOACs. The interview narratives offer some explanation on why secondary care clinicians have such influence. The use of DOACs in secondary care was perceived as an endorsement providing confidence in DOAC therapy to some GPs. It also encouraged GPs to start using DOACs to ensure the same therapy options were offered to patients regardless of the care setting.

At variance with earlier research, this research indicates that the presence of a local champion within primary care (health economy A) was perceived to have a greater impact on the uptake of DOACs than secondary care peers. A champion is defined as “individuals who dedicate themselves, to supporting, marketing and driving through an implementation” (Damschroder et al. 2009, p.11). This observation is in agreement with several implementation frameworks highlighting that the presence of a local champion encourages the uptake of innovation (Damschroder et al. 2009; Greenhalgh et al. 2004).

The present research also adds to the body of knowledge on peer influence by indicating that the choice of DOAC was also influenced by peer prescribing behaviour.
As there are four DOACs available, the interview narratives suggested that the choice of DOAC was influenced by both patient clinical picture and what DOAC was favoured by their peers within their organisation or professional network. The choice of DOAC by peers outside the organisation was suggested to have less impact as DOAC choices by primary and secondary care clinicians differed.

8.8 Compatibility with health economy’s care model

Implementation science recognises the ability and willingness of an organisation to assimilate a health innovation as one of the factors determining the outcome of the implementation (Chaudoir et al. 2013; Damschroder et al. 2009; Greenhalgh et al. 2004; Stetler et al. 2011). This research, in agreement with implementation frameworks (Chaudoir et al. 2013; Damschroder et al. 2009; Stetler et al. 2011) and theory (Greenhalgh et al. 2004), indicated that the willingness of the organisation was shaped by its priorities, implications for existing services, power balances, resources and capacity, and external health system context. Importantly, these findings address the gap identified in the systematic review (Chapter 3) by providing considerable insight into impact of wider organisational and personal attributes identified in this thesis on the uptake of new medicines.

8.8.1 Health economy willingness to assimilate

The findings of this thesis indicated that increasing and achieving optimal anticoagulation of patients with AF was a high clinical priority in all three studied health economies. The DOACs became available in the UK during the time of international and national recognition of growing burden of AF on the healthcare system (Krijthe et al. 2013; Lip et al. 2012; Olesen et al. 2011; Rahman et al. 2014) and inadequate prevention strategies for AF-related strokes (Lip et al. 2012; Medlinskiene and Petty 2017; Rahman et al. 2014). In the UK, it was estimated that 25,000 patients had undiagnosed AF and better diagnosis and optimal use of oral anticoagulants could prevent 7,000 AF-related stroke deaths every year (NICE 2014a). Thus, providing urgency and importance of identifying patients with AF and providing optimal anticoagulation. The interviews indicated that the use of DOACs was seen as a tool to help achieve health economies’ goals regarding AF-care, contributing to their uptake, albeit to a varied extent, across the studied health economies. This agrees with a systematic review of reviews concluding that health innovations fitting with local or
national priorities promote their use (Lau et al. 2015). Also, many implementation frameworks and theories suggest that health innovations’ alignment with the organisation’s priorities and goals support their implementation and use (Chau doir et al. 2013; Damschroder et al. 2009; Greenhalgh et al. 2004; Stetler et al. 2011). However, the results presented in this thesis go beyond previous reports, showing that compatibility with the health economy’s priorities and goals was not sufficient to achieve high uptake of DOACs. Although all three health economies aimed to increase anticoagulation levels and reduce AF-related stroke incidence, the health economy B compared to A and C had slower and lower uptake of DOACs suggesting that other factors came into play in determining the uptake outcome.

The interviews also indicated that the local priorities and prescribing decisions were informed by national health campaigns and changes in national health directives and policies. NICE and European Society of Cardiology (ESC) guidelines were described as supporting the use of DOACs by removing aspirin from recommendations and endorsing DOACs as a therapy option. Recommendations of NICE AF management guidelines were also reflected in updated local formulary and guidelines and some health economies removed the preference of warfarin over DOACs. This is consistent with the systematic review findings (Chapter 3) and a recent study in primary care (Carter et al. 2021) reporting influence of guidelines on prescribing decisions and thus the uptake of new medicines. As reported by Swaithes et al. (2020), the findings of this thesis also indicated that changes to QOF (removing aspirin from therapy options for AF-related stroke prevention) positively affected the use of DOACs. The QOF could be viewed as an incentive scheme as it is a system designed to remunerate general practices for meeting QOF evidence-based indicators for achieving good quality care (Forbes et al. 2017). Some participants attributed greater impact to QOF than NICE AF management guideline as research suggested QOF-related activities were prioritised in primary care (Forbes et al. 2017; Mason 2008; Swaithes et al. 2020).

Also, the interview narratives highlighted that national campaigns led by patient or patient and healthcare professional organisations had an influence on the uptake of DOACs. Patient organisations (Arrhythmia Alliance, AF Association) campaigned for a greater use of DOACs in clinical practice through involvement with the All-Party Parliamentary AF group, supporting local patient AF groups, and providing educational material to both patients and prescribers. This finding adds to the paucity of knowledge
on patient role in the uptake of new medicines as patients through patient organisations were able to exert influence on prescribing and thus the uptake of DOACs.

Moreover, the results in Chapter 6 suggested that perceived low local anticoagulation rates and local populations having a high risk of cardiovascular events were identified as a stimulus for local initiatives promoting the use of oral anticoagulants. Local initiatives across studied health economies used educational events and experts to educate and support clinicians, mainly in primary care, in managing AF and prescribing oral anticoagulants. They differed in intensity, timing, resources. Health economy A was the first out of three studied health economies to deliver a quality improvement project over 18 months, which started in 2012, used existing resources (e.g. peer facilitation, leadership from local GPs, training, information technology support tools) and was a collaboration between GPs, commissioners, local hospitals, and public health teams. The initiative was thought to increase anticoagulation rates by 30% and embed the use of DOACs into GPs practice. The other two health economies delivered educational events and local initiatives after NICE AF management guideline was published. Some study participants also referred to regional and national AF-related campaigns by the Academic Health Science Networks (AHSN), which started in 2015/2016 to increase detection of AF and optimal anticoagulation of patients with AF. Early delivery of a local initiative supporting DOACs use might have contributed to health economy A having the earliest and highest uptake of DOACs compared to the other two areas. Information, education, and training have been noted to support health innovation implementation (Chaudoir et al. 2013; Damschroder et al. 2009; Greenhalgh et al. 2004; Stetler et al. 2011) but the impact of timing of these interventions is relatively unexplored. Although this study finding might suggest that earlier initiatives have a greater impact, further research is required to confirm it.

As proposed by earlier reviews of the implementation of health innovations (Damschroder et al. 2009; Durlak and DuPre 2015; Greenhalgh et al. 2004; Lau et al. 2015), this study’s findings point to collaboration between different stakeholders increasing chances of a successful outcome. Health economies A (quality improvement project) and C (shared local guideline development) took a collaborative approach by involving clinicians from primary and secondary care, commissioners,
and public health representatives in developing and delivering initiatives to promote oral anticoagulant use. Differently to health economy B, a shared vision about the DOACs place in the clinical pathway was noted in health economies A and C and hence a more effective implementation was achieved. Health economies A and C had a consensus that DOACs should be mainly initiated in primary care, whereas health economy B reported disagreement between primary and secondary care regarding who should be initiating these medicines. Furthermore, a more profound tension between decision-makers was suggested by interviews in health economy B. Opponents to DOACs wider use included individuals more strategically placed to control the implementation of DOACs and outnumbered supporters. Disagreements about the value of DOACs caused fragmentation in the rollout of DOACs within the health economy B with some supporters of the innovation implementing DOACs within pockets of their clinical practice, e.g. arrhythmia clinic, specific general practices. As observed in this study, shared vision or collective agreement on goals, value, and purpose of innovation has been proposed to promote (if positive) their uptake (Damschroder et al. 2009; Durlak and DuPre 2015; Greenhalgh et al. 2004; Lau et al. 2015).

8.8.2 Implications for existing services

The results of this research have highlighted that the higher need of resources and complexity of the created clinical pathways had an impact on the uptake of DOACs. Importantly, the findings suggest that the higher the disruption to existing services, the higher the number of resources with increasing intensity were needed to increase the uptake of DOACs.

Although the extent to which health innovations aligned with organisations’ existing services, workflow, and skill mix have previously been suggested to affect their uptake (Damschroder et al. 2009; Greenhalgh et al. 2004; Lau et al. 2015), their impact on new medicine uptake has been under explored (see Chapter 2). In this study, the introduction of DOACs caused a variable degree of disturbance to local services. Before DOACs, the anticoagulation service provision was based on warfarin prescribing and monitoring needs. The introduction of DOACs meant that changes to the current anticoagulation service were needed. Thus, the acceptance of DOACs also depended on how historically warfarin services were delivered and the level of disruption caused by DOACs to these services. The disruption to existing services was
also caused by external context resulting in increasing numbers of patients with AF requiring anticoagulation. Earlier mentioned national campaigns and changes to national policies and guidelines meant that more patients were diagnosed with AF and patients were switched from aspirin to oral anticoagulants.

Interviews suggested that disruption to existing services was low in health economy A, which had faster and higher uptake of DOACs. The anticoagulation service was delivered by primary and secondary care, meaning that clinicians in both settings had expertise in managing anticoagulation and knowledge about AF. Furthermore, the use of rivaroxaban was already embedded in primary care clinical pathway for diagnosis and treatment of deep vein thrombosis, leading to GPs having knowledge and experience in using DOAC therapy. Consequently, the introduction of DOACs for AF did not require profound changes to the existing clinical pathway. Medium disruption was observed in health economy C. Similarly, to health economy A, warfarin services were delivered by primary and secondary care clinicians, but GPs did not have prior experience in using DOACs. The highest disruption was reported in health economy B where anticoagulation service was historically delivered by secondary care. Thus, participants perceived that primary care clinicians had a lack of expertise in managing anticoagulation and the condition and also had no prior experience in using DOACs.

The extent of disruption caused by DOACs to existing services also contributed to decisions on how DOACs would be implemented and thus availability of resources to support their uptake. There was a consensus amongst participants that warfarin services could not be decommissioned or ceased as patients not eligible for DOACs or declining them would need warfarin, thus hindering the uptake of DOACs. It was more notable in health economy B where the warfarin service had been recently reconfigured with substantial investment from commissioners, leading to perceived preference of warfarin over DOACs. Also, health economy B, due to reported lack of shared vision and opposing views outnumbering supporters for DOAC use, were pushed to create a secondary care clinic for DOAC therapy initiation. Consequently, creation of a new clinic resulted in the need for greater resources. Inadvertently, the clinic was perceived as a barrier for DOAC use because it had limited resources and capacity to see a large number of patients and further fuelled the unwillingness of GPs to initiate DOACs in primary care. Contrastingly, in the other two health economies, DOACs were embedded in routine services GPs provide, and thus there was a lower
need of additional resources, likely resulting in greater uptake of DOACs. The participants also suggested that more integrated implementation of DOACs within the existing warfarin service would have promoted the use of DOACs. A suggestion of anticoagulation service, which provided service to both warfarin and DOAC patients, was preferred.

Another important finding is that the shared positive impact of DOACs on services and patient clinical outcomes obtained through local monitoring promoted the uptake of DOACs. For instance, in health economy B the arrhythmia clinic achieved better clinic performance and efficiency with DOAC use, which further strengthened their usefulness and opened discussion for their use in other arrhythmia clinics. In health economy A and C, DOAC use effect was evaluated on patient clinical outcomes and observed positive impact on stroke incidence reduction shared with stakeholders further encouraging the use of DOACs amongst clinicians and commissioners. Patient feedback was also an influence on prescribing decisions.

8.8.3 Local regulations

Greater restrictions to DOAC use communicated through guidelines, policies, and medicine formularies were suggested to be a barrier to their uptake. Health economies B and C described that initially warfarin was preferred over DOACs, but it was more explicit in health economy B as it was also restricted to secondary care initiation. Local policies and formulary conditions were updated to reflect the change in national recommendations, i.e., NICE AF management guideline. However, health economy B indicated that their formal advice was slow to change, likely further contributing to low uptake of DOACs. Interestingly, a recent study examining local medicine formularies of 171 CCGs in 2019 found that a minority, 28 CCGs, still recommended warfarin as a first line oral anticoagulant (Ho et al. 2020). This could be explained by findings in Chapter 6 where participants indicated that interpretation of NICE AF management guideline varied between participants and they were guides for good practice rather than legally binding commissioning statements like NICE technology appraisals. Ho et al.’s (2020) study also concluded that local formulary preference for warfarin over DOACs had no influence on the use of DOACs. Although this study observed lower and slower uptake in health economies where warfarin was proposed as the first line oral anticoagulant, it also indicated that some prescribers were not aware of formulary status or ignored the official local advice, if it did not agree with their view of the best
practice. Hence, the findings lend support to Ho et al.’s (2020) observation that other factors rather than local formularies have a more notable impact on the uptake of DOACs within the studied health economies.

8.9 Pharmaceutical industry role

The results of this thesis indicate that pharmaceutical industry marketing activities influence the uptake of new medicines. There is a long-standing debate on the appropriateness of pharmaceutical industry influence on prescribing decisions and compilation of clinical guidelines. The Pharmaceutical industry is recognised to achieve influence through funding research and publications, direct marketing to clinicians (e.g. meetings with sale representatives), sponsoring promotional, scientific and educational events, direct-to-consumer advertising (not permitted in the UK), or sponsoring patient support groups, and lobbying government officials or providing direct funding to political parties (not permitted in the UK) (Kerwin 2007; Wilcock 2020).

The direct marketing to clinicians through sale representatives (i.e. pharmaceutical detailing) has declined over the years (Pharmaceutical and Life Sciences 2020). Literature reports healthcare organisations and clinicians critiquing such approaches and putting restrictions on access to sale representatives (Anderson et al. 2015; Chressanthis et al. 2012; King et al. 2013; Machanda et al. 2008), this was also echoed in narratives of some participants in this thesis. The direct marketing approaches are well recognised in the literature (see Chapter 2) but the influence of indirect marketing is less well reported (Wilcock 2020).

The research in this thesis adds to the body of knowledge on the indirect marketing influence of pharmaceutical industry on the uptake of new medicines. The interview narratives suggested that pharmaceutical industry used the “resource gaps” created by the limitations of NHS resources to sponsor work that would increase awareness of DOACs or the need of anticoagulation in AF. For instance, the industry provided sponsorship for scientific meetings to develop a guideline for DOAC and warfarin use. The industry also sponsored independent providers to help healthcare organisations to restructure their secondary care anticoagulation service or obtain additional workforce to anticoagulate eligible patients currently not anticoagulated. The aim of all these activities was to improve anticoagulation service and achieve a higher number of eligible patients being offered anticoagulation therapy, which in turn has a potential
to positively contribute to the uptake of DOACs and care of patients. Nevertheless, the benefits and harms of pharmaceutical sponsorship where NHS resources are limited are yet to be determined.

8.10 Strengths and Limitations

The findings and transferability of findings to different settings and patient groups should be considered in the context of the study strengths and limitations. Quality assurance strategies undertaken to reduce limitations of the study were described in Chapter 4. The strengths and limitations of conducted literature reviews and qualitative work are discussed in Chapters 2, 3, 5, and 6. Here, the main strengths and limitations of the overall research described in this thesis will be discussed.

The main strength of this research is that it is the first work underpinned by implementation theory exploring multiple perspectives (patient, healthcare professionals, key stakeholders) in multiple settings on the factors affecting the uptake of new medicines. Thus, the findings provide novel insights and understanding of factors influencing the uptake of new medicines within local health economies and considerations for how identified barriers could be overcome. Another strength of the study was the moderate sample size and recruitment of participants from three health economies with different anticoagulation service provision models. The healthcare professionals and key stakeholders interviewed were from different settings with a varied range of roles. As such, an in-depth exploration of rich and varied experiences was possible, enabling greater insight into potential barriers for DOAC use. However, the author notes that the patient sample comprised almost exclusively White British participants and this is not fully representative of the wider population of the UK.

A further strength of the research is that securing external funding from Pharmacy Research UK, in addition, to support from Leeds Teaching Hospitals NHS Trust allowed facilitation of meaningful PPI throughout the study. The formed advisory PPI group was consulted at each stage of the research and was involved in co-producing study documents, recruitment, data analysis, and dissemination. Furthermore, two supervisors were practising anticoagulation pharmacists and their input allowed identification and recruitment of key participants involved in local decision-making and feasibility of resultant recommendations for practice and policy. Also, data analysis
robustness and validity were increased by including PPI and the supervision team in the process and development of themes and subthemes.

A relative limitation of the study was relying on participants' accounts, which could be affected by recall bias. Participants were asked to describe when oral anticoagulant therapy was started (patients) or implementation of DOACs (prescribers and key stakeholders), which, in most cases, were not recent events. Thus, the interviews may not be an accurate representation of the events that occurred. However, semi-structured interviews allowed exploration of factors that could not be captured by quantitative studies (e.g. innovation-health economy fit).

Lastly, the researcher in this study is a healthcare professional working predominantly in a hospital setting as a pharmacist. Her pre-existing assumptions described in Chapter 4 could have influenced the interview conduct and data analysis. However, the use of the Framework method, involvement of the supervision team and PPI in data analysis made sure that the data analysis and interpretation remained true to the content of interviews as far as this was possible.

8.11 Recommendations for future research

This thesis sets out potential components for toolkit development to improve the uptake of nationally recommended new medicines within local health economies. Future research could employ a co-design approach with healthcare professionals, key stakeholders, and patients to refine the proposed components, identify approaches to address identified barriers in this study, formulate practical and actionable recommendations, and identify resources to support delivery of proposed recommendations. Also, future research could evaluate if the toolkit developed in this thesis by exploring the uptake of DOACs reduces delays in the uptake of nationally recommended new medicines.

Although a range of factors was identified in this study, the environmental impact of new medicines was not referred to in the literature reviews nor the interviews. As the NHS is recognised as the largest public sector contributor to greenhouse emissions in the UK and there is a growing pressure from the public and politics to reduce carbon footprint (Isherwood et al n.d., NHS England and NHS Improvement 2020a, Starup-Hensen et al. 2020), the uptake of a new medicine could be influenced by its carbon footprint. Especially as the NHS has pledged to become a net-zero service by 2050
Initiatives to reduce carbon emissions related to medicines have already been reported. For instance, switching from metered-dose inhalers to dry powder inhalers (Janson et al. 2020, Starup-Hensen et al. 2020). Future studies should explore if new medicines’ carbon footprint influences their uptake. This could be done using quantitative or qualitative research methods.

In March 2020, the WHO declared COVID-19 as a pandemic. This global health emergency had a profound impact on how the NHS services were delivered. For instance, national recommendations stated that patients should be switched to DOACs where possible and patients who needed to have warfarin were offered self-testing of their INR at home to reduce the face-to-face contact (NHS England and NHS Improvement 2020b). This indicates that factors influencing the use of medicines in a pandemic may differ or some factors may have more prominent influence compared to before the pandemic. Future research should explore if and how decision-making on the use of medicines changes during a pandemic. This research should employ qualitative research methods and be informed by implementation frameworks or theory to explore the perspectives of clinicians, key stakeholders, and patients.

8.12 Recommendations for practice and policy

This study has clear implications for practice and policy to improve the uptake of new medicines into practice and thus provided health care to patients.

Firstly, and perhaps the most importantly, patient involvement in decision-making should be facilitated when making therapy decisions. The following should be considered by health organisations and clinicians to overcome the highlighted barriers for patient involvement:

- Provide continuity of ongoing care to build rapport with a patient by allocating a regular clinician or team involved in the patient’s care and familiar with the patient’s clinical picture and needs.
- Lengthen consultation times (especially in primary care) when the decision to start therapy is being made to facilitate discussion of therapy options and address patients’ concerns.
- Provide a periodic review of patients’ satisfaction with their current prescribed therapy and the option to consider alternative therapy options, which potentially
could identify and resolve difficulties patients experience that clinicians might not be aware of.

- Tailor prescribed therapy to patients’ preferences to ensure the therapy fits with their daily lives.

Secondly, decision-makers should consider the following during discussions on new medicines’ availability with local health economies:

- Although assessment of the total costs of new medicines is a complex process, consideration of wider costs applicable to local population should be part of the decision-making discussions. If possible, utilise local health economic models to assess the cost-benefits of the new medicine.

- Where real-world evidence on the efficacy and safety of the new medicine is lacking, decision-makers should consider collecting and providing local data to clinicians and key stakeholders on its effectiveness and safety in clinical practice. Identified concerns with the clinician community should be addressed by utilising local or regional expertise.

- Consider positive and negative effects of the new medicines’ impact on existing services. Also, monitor and provide feedback on service changes during the uptake of new medicine to clinicians and key stakeholders. Both clinicians running the service and patients using the service feedback should be sought and considered.

- Ensure timely update of local policies and guidelines is undertaken in response to national recommendations and policies.

- Resources and support needed to implement the new medicine should be considered, which may include increasing staffing levels, consultation times, and funding.

- Employing a multidisciplinary approach and aiming for a balanced view with supporters and opponents to the use of new medicine. A shared vision on how the new medicine should be used within the health economy should be achieved.

- Training and educational support provided to clinicians (online and/or offline) should be delivered as soon as the new medicine is made available, be continuous and integrated across the health economy.
• Clinical pathways incorporating the new medicine should be made as simple as possible with the least numbers of steps to encourage the use of new medicines.
• Identify a local champion to support and promote the use of new medicine within local clinician communities.
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Appendices

Appendix A Search strategy of the systematic review used for MEDLINE database.

S1. “uptake“
S2. “implement*”
S4. (MH “Diffusion of Innovation” OR diffusion of innovation)
S5. “Sustainability”
S6. S1 OR S2 OR S3 OR S4 OR S5)
S7. “medicine*”
S8. “drug*”
S9. “treatment*”
S10. “medical technolog*”
S11. (MH “Pharmaceutical Preparations” OR pharmaceutical preparation*)
S12. “medical therapy*”
S13. S7 OR S8 OR S9 OR S10 OR S11 OR S12)
S14. “new”
S15. “innovat*”
S16. “novel”
S17. “advance*”
S18. “inventive”
S19. S14 OR S15 OR S16 OR S17 OR S18
S20. (MH “Primary Health Care” OR primary health care)
S21. (MH “Secondary Care” OR MH “Secondary Care Centers” OR secondary care)
S22. “nhs OR national health service”
S23. “clinical commissioning group*”
S24. (MH “General Practice” OR general practitioner practice)
S25. (MH “Family Practice” OR family practice)
S26. (MH “Group Practice” OR group practice OR MH “Hospitals, Group Practice“)
S27. (MH “Health Services” OR health service*)
S28. “hospital* “
S29. (MH “Hospitals”)
S30. S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29
S31. “Barrier*”
S32. “obstacle*”
S33. “imped*”
S34. “challenge*”
S35. “limit*”
S36. “hinder*”
S37. “prevent*”
S38. “inhibit*”
S39. “restrict*”
S40. “enabler*”
S41. “facilitat*”
S42. “access*”
S43. “promot*”
S44. “encourage*”
S45. “stimulat*”
S46. S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45
S47. S6 AND S13 AND S19 AND S30 AND S46
S48. S47 limit to English language
S49. S48 limit to Date of Publication: 2008/01/01-2020/04/23
Appendix B  A search strategy of the narrative review used for MEDLINE database.

S1. (MH “Atrial Fibrillation”)
S2. “atrial fibrillation”
S3. (MH “Stroke”)
S4. “stroke”
S5. S1 OR S2 OR S3 OR S4
S6. “oral anticoagulant”
S7. (MH “Anticoagulants”)
S8. “anticoagulant”
S9. (MH “warfarin”)
S10. “warfarin”
S11. “apixaban”
S12. (MH “Dabigatran”)
S13. “dabigatran”
S14. “edoxaban”
S15. (MH “Rivaroxaban”)
S16. “rivaroxaban”
S17. “non vitamin K antagonist”
S18. “vitamin K antagonist”
S19. (MH “Coumarins”)
S20. “coumarin”
S21. “antithrombotic”
S22. “new oral anticoagulant”
S23. “novel oral anticoagulant”
S24. “NOAC”
S25. “DOAC”
S26. “coumadin”
S27. “acenocoumarol”
S28. “phenprocoumon”
S29. S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28)
S30. (MH “Decision making”)
S31. “decision making”
S32. “shared decision making”
S33. (MH “Patient Participation”) 
S34. “patient participation” 
S35. “patient involvement” 
S36. (MH “Patient preference”) 
S37. “patient preference**” 
S38. “patient choice**” 
S39. “patient decision**” 
S40. (MH “Clinical Decision-Making”) 
S41. “clinical decision making” 
S42. “patient value**” 
S43. “patient view**” 
S44. “patient awareness” 
S45. “patient opinion**” 
S46. “patient treatment preference**” 
S47. (MH “Patient-Centered care”) 
S48. “patient centered care” 
S49. S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48
S50. S5 AND S29 AND S49
S51. S50 limit to English language
Appendix C A poster of narrative literature review presented to the PPI advisory group.

**Are patients with non-valvular AF involved in decision-making about oral anticoagulants?**

A literature review


**BACKGROUND**

Patients with non-valvular atrial fibrillation (AF) are at five-fold increased risk of stroke, which can be prevented with oral anticoagulant therapy. Systematic meta-analysis by Borg et al. (2012) showed that patients had none or little involvement in decision-making about oral anticoagulation therapy. Since the review four new oral anticoagulants, called direct oral anticoagulants (DOACs), were introduced, which may have increased patient’s involvement.

**AIM**

To review the literature to explore if patients with non-valvular AF are involved in decision-making about oral anticoagulant therapy for stroke prevention and to what extent.

**METHOD**

A literature search followed the PRISMA statement (Fig. 1). Search terms were developed from search categories: atrial fibrillation AND oral anticoagulant AND ‘patient involvement.’ The full-text articles were assessed for inclusion by two reviewers independently. Data extraction, quality appraisal using QATSDQ evaluation tool, and analysis was performed by one reviewer.

**RESULTS**

Four studies were conducted in the UK, two in Canada and the remaining in Australia, USA, Denmark, and one across Europe. The methodological quality of studies was varied (scores 13.29 out of 42, median 24.5). Four studies explored patients’ involvement when warfarin was the only oral anticoagulant option and six when warfarin and DOACs were available. Patients’ views were reported in six studies. Four main themes were identified:

1. **Patient involvement in decision-making**
   - Doctors make decisions
   - Active role (encouraged choice)
   - Passive role (it should be this way, an active role desired)
   - Patients don’t trust themselves
   - Lack of information
   - Setting hospital, emergency

2. **Barriers for patient involvement**

3. **Information provision by prescriber**
   - Right or wrong information
   - Influence what information is provided
   - It’s not shared with patients
   - Separation with patients
   - Its patient’s decision

**CONCLUSIONS**

Decision-making is still dominated by prescribers but providing patients with information and available therapy options can promote their involvement in decisions. Further planned work will explore if patient involvement in decision-making has influenced the uptake of DOACs, which has been slow in the UK.
Appendix D Guide used for observation of meetings.

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### DETAILS OF THE MEETING

<table>
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<th>Meeting:</th>
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<tr>
<td>Date:</td>
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<td>Documents collected <em>before</em> the meeting:</td>
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<td>Documents provided <em>during</em> the meeting:</td>
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### SKETCH OF THE ROOM SET UP

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Observation Guide     IRAS ID: 237794     Version 1 06/02/2018
ITEMS TO OBSERVE AND NOTE

1. PROCESS

- How medicine requests for approval are processed?
- Are NICE approved medicines processed differently to non-NICE approved medicines? How?
- What information is used to approve medicines? Who provides this information?
- What actions are set for outside of the meeting in relation to medicine approval or implementation?
- What regulations are set for medicine use? (enablers/supportive, barriers/restrictive) Who decides on these regulations?
- How decisions are communicated to health professionals using medicines, patients?

2. BEHAVIOUR

- Who is leading the approval process?
- Who is engaging/contributing to the process?
- Is anyone influencing the process?
- How responsibilities are shared?
- Dynamics
- Interactions

3. ANY OTHER RELAVANT INFORMATION
Appendix E Process flowchart of a DOAC inclusion to the medicine formularies at Health Economy C. It was valid at the time of DOACs introduction.

Clinician completes a pre-specified submission form

The application is reviewed by the Medicine Information (MI) pharmacy team
(Patient safety, clinical effectiveness, cost effectiveness or resource impact, strength of evidence, place in therapy relative to available treatments, national guidance and priorities, local health priorities, equity of access).

Primary Care opinion

Returned for further clarification

Application validated for submission to Trust Drug and Therapeutic Committee (DTC)

Application discussed at Trust DTC meeting with/without the clinician attending
Committee members include representatives from MI pharmacy team, Area Prescribing Group (APG)/Clinical Commissioning Group, specialty physicians.

Request approved

Medicine included in the Trust formulary

CCG formulary group
The group make decisions such as traffic light classification, formulary additions, and present the case to the APG.

Submitted for approval or ratification

Developed joint primary and secondary care guidance: stroke prevention in non-valvular AF

The AF interest group
Group members include clinicians from secondary and primary care, medicine management and governance pharmacists, public health representative.

Application discussed at APG meeting
Committee members include clinicians (physicians and Chief pharmacist) from local Trusts, representatives from CCG medicine management team, CCG clinical audit effectiveness team, local medical committee, local pharmaceutical committee, non-medical prescriber, general practitioners, and a lay member.

Medicine included in the primary care formulary
Appendix F Participant information sheet for observation of meetings.

Participant Information Sheet  IRAS ID: 237794

A study of barriers and enablers in the introduction of direct oral anticoagulants approved by NICE into patient care

We would like to invite you to take part in our research study. This information sheet tells you the purpose of the study and what your participation would involve. Before you decide whether to take part, it is important that you understand why the research is being done and what it will involve.

Please take time to read the following information carefully to help you decide whether to take part. You can discuss this information with others if you wish. If you wish to discuss this study further or have any questions, feel free to contact the researcher on 01274 232382.

What is the purpose of this study?
This study aims to investigate what helps and prevents the use of innovative medicines such as direct oral anticoagulants (DOACs) approved by NICE into patient care. The study will be conducted in [insert name of meeting] as it has several different work streams but this one focuses on the process and decision-making on implementation of DOACs within local health economies.

Observing how decisions are made on implementation of medicines at [insert name of meeting] meetings will be highly valuable.

About the observation
If you agree, the researcher will attend to observe up to three [insert name of meeting] meetings and take notes. No personal information will be collected from participants. The researcher will sit or stand somewhere out of the way and thus will not interfere with your work. If you want the researcher to stop observing or leave the room, you can ask them to do so at any time.

Will the information I give be kept confidential?
Yes. All data will be kept safely and will not be revealed to third parties without your explicit permission and will not be transferred overseas, in accordance with the 1998 Data Protection Act and, after 26 May 2018, the General Data Protection Regulation. All information collected during observations will be anonymised and unidentifiable participant codes will be used instead.

All data will be stored on password-protected server or in locked cabinets at the University of Bradford.

We may use information from observations in reports, publication, or any other means of dissemination of findings, but these will not be linked to individual participants in the meetings.

What are the benefits of taking part?
The information from this study will help to make recommendations to improve current practice and ensure that all patients have access to innovative medicines approved by NICE regardless where they live.

What are disadvantages of taking part?
We do not anticipate any problems arising from participation in this study. We will not ask you to change anything about the way you work.
Participant Information Sheet  IRAS ID: 237794

Do I have to take part?
It is up to you to decide to join the study. You do not have to give a reason. You are free to change your mind up to two weeks after the observation, without giving a reason.

What will happen to the findings of this study?
We will use the information from observations to develop process maps of implementation of innovative medicines approved by NICE such as DOACs within local health economies. These process maps will be sent to internal medicine information pharmacists for review to test their accurateness. Also, collected information will inform interviews later in the study.

The study findings will be published in academic journals or presented in meetings and conferences. Individual participants will not be identified in any published reports, journal articles, or presentations. Also, organisation names will not be used in any published reports, journal articles or presentations. However, the organisation maybe identified from the context.

Collected identifiable information will be securely destroyed within 12 months after completion of the study. All anonymised data gathered during the study will be securely destroyed 5 years after completion of the study.

Who has reviewed this study?
This study has been reviewed by Health Research Authority NHS Research Ethics, University of Bradford, Leeds Teaching Hospitals NHS Trust, and patient and public representatives.

Who is organizing and funding the research?
This research is part of a PhD project by Kristina Medinskiene at University of Bradford. The study is sponsored by University of Bradford and funded by Leeds Teaching Hospitals NHS Trust.

Where can I find out further information?
For further information, please contact the lead researcher: Kristina Medinskiene 01274 232382 or email k.medinskiene1@bradford.ac.uk

Will I be contacted again?
We will send you up to two reminders to consider the participation in the study.

Thank you for considering taking part in this study

If you have any concerns or complains related to your participation in this study please contact
the researcher or the Principal Supervisor:

Dr Duncan Petty 01274 236594
d.r.petty1@bradford.ac.uk

Alternatively, you can contact the Information Commissioner’s Office on 0303 123 1113

Observations
Appendix G Consent form for observation of meetings.

Observation of [insert name] meetings
A study of barriers and enablers in the introduction of direct oral anticoagulants approved by NICE into patient care

Please read each of the following points, initial each box and provide ‘YES’ or ‘NO’ answer in each box. Just ask if there is anything you don’t understand or you are unsure about.

Please initial and provide ‘YES’ or ‘NO’ answer in each box

1. I have read and understand the information sheet dated 06/06/2018 (Version 3).

2. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

3. I understand if I want the researcher to stop observing or leave the room, I can ask them to do so at any time.

4. I understand that during observations the researcher will not interfere with the meeting.

5. I understand that information from observations may be used in publications and presentations, but these will not be linked to individual participants in the meetings.

6. I understand that the name of the organisation will not be used in any publications or presentations, but the organisation may be identified from the context.

7. I understand that all data collected about participants in the meetings will be kept confidentially and securely.

8. I understand that I can withdraw from the study up to two weeks after the observation and the observation data will not be used in the study. However, if I withdraw from the study two weeks after the observation, the researcher will keep the information about the observation that they have already obtained.

9. I agree for the meetings to be observed by the researcher.

10. I would like to receive the summary of the study findings.

11. I agree for individuals from regulatory organisations and University of Bradford to look at research records containing anonymised observation notes to check the accuracy of the research study.

Name of the participant (PRINT) Date Signature

Researcher (PRINT) Date Signature

Office use
Participant ID number for study: ...................................................................................................................
One copy to the researcher and one copy to the participant

Observations Consent Form V3 06/06/2016
Appendix H Patient interview guide.

Interview Guide: Group 1 participants

[Turn recorded on]

Introduction and confirm consent given.

1. Tell me about your blood-thinning medicine (oral anticoagulant). Oral anticoagulant would be warfarin, rivaroxaban (Xarelto), apixaban (Eliquis), dabigatran (Pradaxa), edoxaban (Lixiana), acenocoumarol, phenindione. (Use additional sheet with pictures).
   a) Which oral anticoagulant are you taking?
   b) How long have you been taking it?
   c) Do you know what it is for?
   d) What is your experience on being this medicine?
   e) Have you been on any other blood-thinning medicine?

2. What was your experience of the consultation when you were told about X (oral anticoagulant)?
   a) What led you to needing this medicine?
   b) Who was the consultation with?
   c) Can you remember what information you were given at the time? Were you given information later?

3. Who do you think made the decision which oral anticoagulant you should take?
   a) Did you have any say? If yes, who initiated your involvement?
   b) If no, did you want to be involved? What prevented you to be involved?
   c) If you didn’t want to be involved, why?

4. Where you aware of other available blood-thinning medicines?
   If yes:
   a) How did you find out?
   b) Where you offered a choice? If yes, how did you choose?

5. There are 3 different consultation ways (use additional info sheet):
   a) Do you remember what happened during your consultation?
   b) Which approach do you prefer? Why?

6. What do you think is required for patients to be involved in the decision-making process?

7. What do you think stops the use of new approved medicines in the NHS? Why?

8. Looking back at what we talked about, is there something you wish to add?

Thank you for your time.
[Turn recorder off]

IRAS ID: 237794

Version 1.1 03/08/2018
Appendix I Healthcare professional interview guide.

Interview Guide: Group 2 participants

Health professional
1. Tell me about your role in care of patient with atrial fibrillation and taking oral anticoagulants.
   a) Do you prescribe or advice on oral anticoagulants?
      ▪ How do you make the decision, which oral anticoagulant to prescribe/recommend?
      ▪ What influences your decision? Are your choices limited and how?
      ▪ Do you use local guidelines/policies? What is your view on local guidelines/policies/shared-agreement?

2. Whose responsibility do you think is to offer oral anticoagulants to patients with atrial fibrillation? Offer to change to a different oral anticoagulant? Start treatment?
   b) If someone else, why? What is your role in such scenario?
   c) What about patients taking warfarin and who are monitored outside your practice?

Patient
3. What is the role of the patient in your decision-making process?

4. Do you think all patients are presented with same oral anticoagulant options? Why?

Organisation
4. Why do you think the use of DOACs is varied across different CCGs?

5. Is there anything that prevents or encourages you to prescribe/recommend DOACs in your practice?

6. What do you think stops or promotes the use of new medicines approved by NICE in the NHS?

7. Why do you think the uptake of DOACs was slower than expected? How can it be improved?

8. Looking back at what we talked about, is there anything you wish to add?

Thank you for your patience.

Version 0.2 14/12/17
Appendix J Key stakeholder interview guide.

Interview Guide: Group 3 participants

Organisation
1. Tell me about your role in implementing medicines approved by NICE at local organisations.
   ▪ Who else is involved in implementing these medicines at your organisation/area?

2. What do you think stops or promotes the use of new medicines approved by NICE in your organisation/area?
   ▪ How health professionals are informed about such medicines?
   ▪ What could be done to improve the safe uptake of innovative medicines approved by NICE like DOACs in your organisation?
   ▪ Do guidelines/policies/formulary supports or limits the use of such medicines? How?

DOACs/NOACs
3. Why do you think the use of DOACs/NOACs is varied across different CCGs?
   ▪ What promotes the use of DOACs? What limits the use of DOACs?

4. Why do you think the uptake of DOACs was slower than expected? What were the factors?
   ▪ What do you think about the uptake of DOACs in your organisation/area? Is there anything that prevents or encourages the use of DOACs?

5. Looking back at what we talked about, is there anything you wish to add?

Thank you for your patience.

Version 0.2 14/12/17
Appendix K Patient information leaflet.

Your medical notes may be accessed by the NHS Trust Research & Development team for audit purposes.

9. What will happen to the findings of the study?
Your role in this study will end after one meeting. We will then take the information you and others have given us to understand the role of patients in decision-making about use of blood-thinning medicines.
We will write a report summarising findings. If you wish, we can give you a copy of the report. We will publish the study findings in academic journals. Quotes from you interview, from which you will not be identified, may be used with your permission. You will not be identified in any published report or journal articles.

10. What if I want to know more about the study?
If there is anything you are not sure about, or if you have any questions, please contact the researcher. Contact details are on the front and back of this leaflet.

11. Who has reviewed this study?
This study has been reviewed by the NHS Research Ethics Committee, University of Bradford, Leeds Teaching Hospitals NHS Trust, and patient and public representatives.

12. Who is funding this study?
The University of Bradford is the sponsor for this study based in United Kingdom. The study is funded by Leeds Teaching Hospitals NHS Trust.

13. What if I have a complaint about the study?
If you want to make a complaint about the study you can contact the researcher or the Principal Supervisor, Dr Duncan Petty (01274 236594), at the University of Bradford.
If you want to complain at any point during the study to an independent body you can contact your local Patient Advice Liaison Service (PALS) by telephoning [local PALS number] or the Information Commissioner’s Office on 030 123 113

14. Thank you
You will receive a £10 gift card as a token of appreciation for taking part.

Interested or want to find out more?
Please contact Kristina (the researcher) at: k.medlinskiene1@bradford.ac.uk 01274 232382

THANK YOU!

Patient involvement in decision-making about oral anticoagulants for stroke prevention in atrial fibrillation

Contact us:
Kristina Medlinskiene, the researcher:
- Telephone: 01274 232382
- E-mail: k.medlinskiene1@bradford.ac.uk
- Post: M24 Richmond Building, University of Bradford, BD7 1DP

1. Why have I been chosen?
We are inviting patients with atrial fibrillation (AF) who are taking blood-thinning medicines (warfarin, acenocoumarol, phenindione, rivaroxaban, dabigatran, apixaban or edoxaban) to take part in new research about their experiences.

2. Why are we doing this study?
AF-related stroke risk can be reduced with blood-thinning medicines. Warfarin, a traditional blood-thinning medicine, has been used for many years. In the past five years, direct oral anticoagulants (DOACs or NOACs) have been introduced.
6. How can I be involved?

- Read this information sheet
- Contact us to express your interest or if you have any questions
- Researcher will answer your questions about the study
- Complete a consent form
- Researcher will contact you to arrange a meeting
- Meet with the researcher (up to 60 minutes)

7. Are there drawbacks of taking part?

Your time for the meeting. It may last up to 60 minutes. We will work with you to ensure this is done at a time that suits you. There will be no direct risks or disadvantage in taking part.

8. Will the information I give be kept confidential?

Yes. The audio recording of the meeting will be securely transported to the University of Bradford. It will be stored safely in the research office. The record will only be shared with professional transcribing agency for transcribing it into a written format. Any personal identifiers will be removed – which means you will not be identifiable in any way. The record will be destroyed after transcribing.

If you agree, anonymous quotes from your discussions with the researcher may be included when we share the findings of the study, in either written or spoken form.

Identifiable information (name, gender, age, ethnicity and your contact details) will be collected and securely stored at the University of Bradford. Personal data will not be passed on or transferred overseas. It will be securely destroyed within 12 months after the study ends. All anonymized data will be securely destroyed 5 years after the study ends.

Register your interest today and be part of the research!
Appendix L Patient consent form.

Do you consent to take part in the study?

Patient involvement in decision-making about oral anticoagulants for stroke prevention in atrial fibrillation

Please read each of the following points, initial each box and provide ‘YES’ or ‘NO’ answer in each box. Just ask if there is anything you don’t understand or you are unsure about.

Please initial and provide ‘YES’ or ‘NO’ answer in each box

1. I have read and understand the information sheet version dated 21/02/2018 (Version 1).
2. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
3. I understand that my participation is voluntary. I am free to withdraw up to two weeks after the interview without giving any reason, and without my medical care being affected.
4. I understand that should I not wish to answer any particular question or questions, I am free to decline.
5. I understand that my interview will be audio-recorded and that anonymous quotes may be used in reports and publications about the research.
6. I understand that all data collected about me will be kept confidentially and securely.
7. I agree to take part in this interview.
8. I would like to receive the summary of the study findings.

Name of participant (PRINT) Date Signature

Researcher (PRINT) Date Signature

Please turn over
Name of Researcher: Kristina Medlinskiene

**Participant details** (these will only be used for the purpose of the study and be stored securely)

Please provide contact details for the researcher to contact you to arrange the interview:

Full name

Telephone number (home)

OR

Telephone number (mobile)

OR

E-mail address

OR

Postal address

**Office use**

Participant ID number for study

One copy to the researcher and one copy to the patient
Participant Information Sheet    IRAS ID: 237794

A study of barriers and enablers in the introduction of direct oral anticoagulants approved by NICE into patient care

We would like to invite you to take part in our research study. This information sheet tells you the purpose of the study and what your participation would involve. Before you decide whether to take part, it is important that you understand why the research is being done and what it will involve.

Please take time to read the following information carefully to help you decide whether to take part. You can discuss this information with others if you wish. If you wish to discuss this study further or have any questions, feel free to contact the researcher on 01274 232382.

What is the purpose of this study?
This study aims to investigate what helps and prevents the use of innovative medicines such as direct oral anticoagulants (DOACs) approved by NICE into patient care. DOACs are used for stroke prevention in patients with non-valvular atrial fibrillation. However, their introduction into patient care in the UK has been slower than expected and varied across different clinical commissioning groups. The study will be conducted in a site it has several different work streams but this one focuses on healthcare professionals' views and experiences.

Why have I been invited?
You have been invited because you are involved in care of patients with atrial fibrillation taking oral anticoagulants.

What will be involved if I choose to take part in this study?
If you agree to take part, you will need to sign a consent form included in this pack and return it to the researcher. The researcher will contact you to arrange a face-to-face interview at a place and time that is convenient for you or over the telephone.

The interview will be audio recorded and last up to 45 minutes. During the interview the researcher will ask you to share your views on barriers on the use of innovative medicines approved by NICE like DOACs in your practice.

Will the information I give be kept confidential?
Yes. All data will be kept safely and will not be transferred overseas, in accordance with the 1998 and, after 26 May 2018, the General Data Protection Regulation. The interview record will only be shared with the professional transcribing agency for transcribing it into a written form. All information collected during the interview will be anonymised and unidentifiable participant codes will be used instead.

If persons and organisations are mentioned during the interview these will be not be transcribed or used. Personal information (i.e name and contact details) will be available to the researcher involved in data collection only, and used only for the purpose of contacting you. All data will be stored on password-protected server or in locked cabinets at the University of Bradford. Personal information will be securely destroyed within 12 months and anonymized data 5 years after the study ends.

With your permission, we may use quotes from your interview in reports, publication, or any other means of dissemination of findings, but these will not be linked to you or your organisation.

Group 2 participants

Version 5 27/06/19
Participant Information Sheet  IRAS ID: 237794

Will I be paid to take part in this study?
There is no payment for your participation but we will offer reimbursement for your travel expenses, if required.

What will happen to the findings of this study?
Your role in this study will end after one interview. We will then take the information you and others have given us to understand barriers for use of DOACs within local health economies.
The study findings will be published in academic journals or presented in meetings and conferences. With your permission, anonymous quotes from the interview may be included when we share the findings of the study, in either written or spoken form.
You or your organisation will not be identified in any published reports, journal articles, or presentations. However, your organisation may be identified from the context.

Do I have to take part?
It is up to you to decide to join the study. You do not have to give a reason. You are free to change your mind up to two weeks after the interview, without giving a reason.

What are the benefits of taking part?
The information from this study will help to make recommendations to improve current practice and ensure that all patients have access to innovative medicines approved NICE such as DOACs regardless where they live.

Who has reviewed this study?
This study has been reviewed by Health Research Authority NHS Research Ethics, University of Bradford, Leeds Teaching Hospitals NHS Trust, and patient and public representatives.

Who is organizing and funding the research?
This research is part of a PhD project by Kristina Medlinskiene at the University of Bradford. It is sponsored by University of Bradford and funded by Leeds Teaching Hospitals NHS Trust and Pharmacy Research UK.

Where can I find out further information?
For further information, please contact the lead researcher: Kristina Medlinskiene 01274 232382 or email k.medlinskiene1@bradford.ac.uk

Will I be contacted again?
We will send you up to two reminders to consider the participation in the study.

Thank you for considering taking part in this study

If you have any concerns or complaints related to your participation in this study please contact the researcher or the Principal Supervisor:

Dr Duncan Petty 01274 236594
d.r.petty1@bradford.ac.uk
Alternatively, you can contact the Information Commissioner’s Office on 0303 123 1113
Appendix N Healthcare professional consent form.

<table>
<thead>
<tr>
<th>IRAS ID: 237794</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of Researcher: Kristina Medlinskiene</td>
</tr>
</tbody>
</table>

**Do you consent to take part in the study?**

A study of barriers and enablers in the introduction of direct oral anticoagulants approved by NICE into patient care

Please read each of the following points, initial each box and provide ‘YES’ or ‘NO’ answer in each box. Just ask if there is anything you don’t understand or you are unsure about.

Please initial and provide ‘YES’ or ‘NO’ answer in each box

<table>
<thead>
<tr>
<th>1. I have read and understand the information sheet version dated 27/06/2019 (Version 5).</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.</td>
</tr>
<tr>
<td>3. I understand that my participation is voluntary. I am free to withdraw up to two weeks after the interview.</td>
</tr>
<tr>
<td>4. I understand that should I not wish to answer any particular question or questions, I am free to decline.</td>
</tr>
<tr>
<td>5. I understand that my interview will be audio-recorded and I give permission for anonymous quotes from my interview to be used in reports and publications about the research.</td>
</tr>
<tr>
<td>6. I understand that all data collected about me will be kept confidentially and securely.</td>
</tr>
<tr>
<td>7. I agree to take part in this interview.</td>
</tr>
<tr>
<td>8. I would like to receive the summary of the study findings.</td>
</tr>
<tr>
<td>9. I agree for individuals from regulatory organisations and University of Bradford to look at research records containing my anonymised interview to check the accuracy of the research study.</td>
</tr>
</tbody>
</table>

Name of participant (PRINT)  Date  Signature

Researcher (PRINT)  Date  Signature

Interview Consent Form: Groups 2, 3 and 4  V4 27/06/2019 1
Participant details (these will only be used for the purpose of the study and be stored securely)

Please provide contact details for the researcher to contact you to arrange the interview:

Full name........................................................................................................................................

Telephone number (home)............................................................................................................

OR

Telephone number (mobile)............................................................................................................

OR

E-mail address...................................................................................................................................

OR

Postal address....................................................................................................................................

Office use

Participant ID number for study........................................................................................................

One copy to the researcher and one copy to the participant
Appendix O Social media recruitment flyers used for healthcare professionals.

A study of barriers and enablers in the introduction of direct oral anticoagulants approved by NICE into patient care

- Are you a doctor, a nurse or a pharmacist?
- Are you involved in care of patients with non-valvular atrial fibrillation requiring oral anticoagulants for stroke prevention?
- Do you practice in [redacted]?

If you answer YES to all 3 questions, we would like to invite you to take part in this research study.

What will I do?
Participate in one interview about your views on barriers on the use of innovative medicines approved by NICE like DOACs in your practice.

If you want to find out more or take part, please contact Kristina (the researcher) for more information:
01274 236594
k.medlinskiene1@bradford.ac.uk

Thank you!
Appendix P Key stakeholder information sheet.

A study of barriers and enablers in the introduction of direct oral anticoagulants approved by NICE into patient care

We would like to invite you to take part in our research study. This information sheet tells you the purpose of the study and what your participation would involve. Before you decide whether to take part, it is important that you understand why the research is being done and what it will involve.

Please take time to read the following information carefully to help you decide whether to take part. You can discuss this information with others if you wish. If you wish to discuss this study further or have any questions, feel free to contact the Researcher on 01274 232382.

What is the purpose of this study?
This study aims to investigate what helps and prevents the use of innovative medicines such as direct oral anticoagulants (DOACs) approved by NICE into patient care. DOACs are used for stroke prevention in patients with non-valvular atrial fibrillation. However, their introduction into patient care in the UK has been slower than expected and varied across different clinical commissioning groups. The study will be conducted in [redacted]. It has several different work streams but this one focuses on views of NHS staff involved in implementation of DOACs.

Why have I been invited?
You have been invited because you are involved in implementation of innovative medicines approved by NICE like DOACs within your local health economy.

What will be involved if I choose to take part in this study?
If you agree to take part, you will need to sign a consent form included in this pack and return it to the researcher. The researcher will contact you to arrange a face-to-face interview at a place and time that is convenient for you or over the telephone.

The interview will be audio recorded and last up to 45 minutes. During the interview the researcher will ask you to share your views on barriers and enablers on the use of innovative medicines approved by NICE like DOACs in your organization.

Will the information I give be kept confidential?
Yes. All data will be kept safely and will not be transferred overseas, in accordance with the 1998 and, after 26 May 2018, the General Data Protection Regulation. The interview record will only be shared with the professional transcribing agency for transcribing it into a written form. All information collected during the interview will be anonymised and unidentifiable participant codes will be used instead.

If persons and organisations are mentioned during the interview these will be not be transcribed or used. Personal information (i.e. name and contact details) will be available to the researcher involved in data collection only, and used only for the purpose of contacting you. All data will be stored on password-protected server or in locked cabinets at the University of Bradford. Personal information will be securely destroyed within 12 months and anonymized data 5 years after the study ends.

With your permission, we may use quotes from your interview in reports, publication, or any other means of dissemination of findings, but these will not be linked to you or your organisation.
Will I be paid to take part in this study?
There is no payment for your participation but we will offer reimbursement for your travel expenses, if required.

What will happen to the findings of this study?
Your role in this study will end after one interview. We will then take the information you and others have given us to understand barriers for use of innovative medicines approved by NICE.

The study findings will be published in academic journals or presented in meetings and conferences. With your permission, anonymous quotes from the interview may be included when we share the findings of the study, in either written or spoken form.

You or your organisation will not be identified in any published reports, journal articles, or presentations. However, your organisation may be identified from the context.

Do I have to take part?
It is up to you to decide to join the study. You do not have to give a reason. You are free to change your mind up to two weeks after the interview, without giving a reason.

What are the benefits of taking part?
The information from this will help to make recommendations to improve current practice and ensure that all patients have access to innovative medicines approved by NICE such as DOACs regardless where they live.

Who has reviewed this study?
This study has been reviewed by Health Research Authority NHS Research Ethics, University of Bradford, Leeds Teaching Hospitals NHS Trust, and patient and public representatives.

Who is organizing and funding the research?
This research is part of a PhD project by Kristina Medlinskiene at the University of Bradford. The study is sponsored by University of Bradford and funded by Leeds Teaching Hospitals NHS Trust and Pharmacy Research UK.

Where can I find out further information?
For further information, please contact the lead researcher: Kristina Medlinskiene 01274 232382 or email k.medlinskiene1@bradford.ac.uk

Will I be contacted again?
We will send you up to two reminders to consider the participation in the study.

Thank you for considering taking part in this study
If you have any concerns or complains related to your participation in this study please contact the researcher or the Principal Supervisor:

Dr Duncan Petty 01274 236594
d.r.petty1@bradford.ac.uk
Alternatively, you can contact the Information Commissioner’s Office on 0303 123 1113
Appendix Q Pharmaceutical industry information sheet.

Participant Information Sheet  IRAS ID: 237794

A study of barriers and enablers in the introduction of direct oral anticoagulants approved by NICE into patient care

We would like to invite you to take part in our research study. This information sheet tells you the purpose of the study and what your participation would involve. Before you decide whether to take part, it is important that you understand why the research is being done and what it will involve.

Please take time to read the following information carefully to help you decide whether to take part. You can discuss this information with others if you wish. If you wish to discuss this study further or have any questions, feel free to contact the Researcher on 01274 232382.

What is the purpose of this study?
This study aims to investigate what helps and prevents the use of direct oral anticoagulants (DOACs) approved by NICE into patient care. DOACs are used for stroke prevention in patients with non-valvular atrial fibrillation. However, their introduction into patient care in the UK has been slower than expected and varied across different clinical commissioning groups. The study will be conducted in Leeds, Bradford, and Sheffield. It has several different work streams but this one focuses on pharmaceutical industry representatives’ views on barriers and enablers to the use of DOACs within local health economies.

Why have I been invited?
You have been invited because you represent a pharmaceutical company that supplies DOACs in the UK and thus have been involved in implementation of DOACs at Bradford, Leeds or Sheffield areas.

What will be involved if I choose to take part in this study?
If you agree to take part, you will need to sign a consent form included in this pack and return it to the researcher. The researcher will contact you to arrange a face-to-face interview at a place and time that is convenient for you or over the telephone.

The interview will be audio recorded and last up to 45 minutes. During the interview the researcher will ask you to share your views on barriers and enablers on the use of DOACs in Bradford, Leeds or Sheffield health economies.

Will the information I give be kept confidential?
Yes. All data will be kept safely and will not be transferred overseas, in accordance with the 1998 and, after 26 May 2018, the General Data Protection Regulation. The interview record will only be shared with the professional transcribing agency for transcribing it into a written form. All information collected during the interview will be anonymised and unidentifiable participant codes will be used instead.

If persons and organisations are mentioned during the interview these will be not be transcribed or used. Personal information (i.e. name and contact details) will be available to the researcher involved in data collection only, and used only for the purpose of contacting you. All data will be stored on password-protected server or in locked cabinets at the University of Bradford. Personal information will be securely destroyed within 12 months and anonymized data 5 years after the study ends. With your permission, we may use quotes from your interview in reports, publication, or any other means of dissemination of findings, but these will not be linked to you or your organisation.
Participant Information Sheet  IRAS ID: 237794

Will I be paid to take part in this study?
There is no payment for your participation but we will offer reimbursement for your travel expenses, if required.

What will happen to the findings of this study?
Your role in this study will end after one interview. We will then take the information you and others have given us to understand barriers for use of innovative medicines approved by NICE.

The study findings will be published in academic journals or presented in meetings and conferences. With your permission, anonymous quotes from the interview may be included when we share the findings of the study, in either written or spoken form but these will not be linked to you or your organization.

You or your organisation will not be identified in any published reports, journal articles, or presentations. However, your organization maybe identified from the context.

Do I have to take part?
It is up to you to decide to join the study. You do not have to give a reason. You are free to change your mind up to two weeks after the interview, without giving a reason.

What are the benefits of taking part?
The information from this study will help to make recommendations to improve current practice and ensure that all patients have access to innovative medicines approved by NICE such as DOACs regardless where they live.

Who has reviewed this study?
This study has been reviewed by Health Research Authority NHS Research Ethics, University of Bradford, Leeds teaching Hospitals NHS Trust, and patient and public representatives.

Who is organizing and funding the research?
This research is part of a PhD project by Kristina Medlinskiene at the University of Bradford. The study is sponsored by University of Bradford and funded by Leeds Teaching Hospitals NHS Trust and Pharmacy Research UK.

Where can I find out further information?
For further information, please contact the lead researcher: Kristina Medlinskiene 01274 232382 or email k.medlinskiene1@bradford.ac.uk

Will I be contacted again?
We will send you up to two reminders to consider the participation in the study.

Thank you for considering taking part in our study

If you have any concerns or complains related to your participation in this study please contact the researcher or the Principal Supervisor:

Dr Duncan Petty 01274 236594
d.r.petty1@bradford.ac.uk

Alternatively, you can contact the Information Commissioner’s Office on 0303 123 1113
### Appendix R Analytical framework developed for interviews with patients.

**Analytical framework (interviews with patients)**

1. **PATIENT MEDICAL BACKGROUND AND MEDICINES**
   - a. Demographic information
   - b. Description of events leading to needing OAC
   - c. Experience with and feelings about OACs
   - d. Changes to medicines (OAC and other)
   - e. Other

2. **CONSULTATION EXPERIENCE**
   - a. Consultation experience and patient participation
   - b. Choice of OAC
   - c. Sources of information and information given, including prior knowledge about OACs
   - d. Other healthcare professionals’ involvement and follow up

3. **WAYS TO IMPROVE CONSULTATIONS**
   - a. Preferred consultation type and description of patient and HCP roles
   - b. Factors affecting patient’s involvement

4. **FACTORS AFFECTING NEW MEDICINE USE**
   - a. Factors affecting new medicine use

5. **OTHER**

*OAC= oral anticoagulant, HCP= healthcare professional*
Appendix S Analytical framework for interviews with key stakeholders and healthcare professionals.

1. INTERVIEWEE INFORMATION
   a. Role

2. MEDICINE-LEVEL FACTORS
   a. Efficacy
   b. Safety concerns
   c. Cost considerations
   d. Complexity to use
   e. Nature of knowledge required
   f. Availability from manufacturer

3. PATIENT-LEVEL FACTORS
   a. Socio-demographic characteristics
   b. Health status
   c. Engagement with treatment
   d. Role in consultations

4. PRESCRIBER-LEVEL FACTORS
   a. Socio-demographic characteristics
   b. Scope of expertise & knowledge (skills)
   c. Prescribing habits & therapy preferences
   d. Social networks influence

5. ORGANISATION-LEVEL FACTORS
   a. Organisation characteristics (size, location & type)
   b. Available services & resources
   c. Available OAC & formulary conditions
   d. Local guidelines
   e. Implementation process

6. EXTERNAL ENVIRONMENT-LEVEL FACTORS
   a. Pharmaceutical industry
   b. External peer influence, opinion leaders, & champions
   c. External guidelines
   d. Other information sources
   e. Collaborations & affiliations
   f. Other Health Economies

7. OTHER

*OAC = oral anticoagulants
Appendix T Health Research Authority approval.

Mrs Kristina Medlinskiene
M24 office, Richmond Building
Richmond road, University of Bradford
Bradford
BD7 1DP
k.medlinskiene1@bradford.ac.uk

20 June 2018

Dear Mrs Medlinskiene

Study title: A study of barriers and enablers in the introduction of direct oral anticoagulants approved by NICE into patient care
IRAS project ID: 237704
Protocol number: N/A
REC reference: 18/SC/0284
Sponsor: University of Bradford

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales? You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations in England and Wales that are recruiting patients should formally confirm their capacity and capability to undertake the study. How this will be confirmed is detailed in the “summary of assessment” section towards the end of this letter. You should then work with each organisation that has confirmed capacity and capability and provide clear instructions when research activities can commence.

Participating NHS organisations in England and Wales that are recruiting NHS staff will not be required to formally confirm capacity and capability before you may commence research activity at site. As such, you may commence the research at each organisation 35 days following sponsor provision to the site of the local information pack, so long as:
- You have contacted participating NHS organisations (see below for details)
- The NHS organisation has not provided a reason as to why they cannot participate
Appendix U NHS Research Ethics Committee approval.

Health Research Authority
South Central - Oxford B Research Ethics Committee

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

19 June 2018

Mrs Kristina Medlinskiene
M24 office, Richmond Building
Richmond road, University of Bradford
Bradford
BD7 1DP

Dear Mrs Medlinskiene

Study title: A study of barriers and enablers in the introduction of direct oral anticoagulants approved by NICE into patient care

REC reference: 18/SC/0284
Protocol number: N/A
IRAS project ID: 237794

Thank you for your letter of 8th June 2018, responding to the Proportionate Review Sub-Committee’s request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact please contact hra.studyregistration@nhs.net outlining the reasons for your request.
Appendix V Non-substantial amendment approval.

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<th>Amendment Categorisation and Implementation Information</th>
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<tr>
<td>Dear Mrs Medlinskiene,</td>
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<td>IRAS Project ID:</td>
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For NHS/HSC R&D Office Information