Access to Medicines in the United Kingdom

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**Abstract**

The aim of this research project was to assess the access to medicines situation in the United Kingdom. The project begins with a systematic review of the literature to explore current knowledge, which identified the need for further comparative studies to explore access to medicines across the United Kingdom. Two mixed-methods studies were conducted to investigate this issue.

The research methods employed include a systematic review of the literature, document analysis of publicly available records and literature (Study 01), and semi-structured interviews with relevant experts to project the situation of access to medicines in the UK (Study 02). The research objectives were based on the findings from the systematic literature review.

The findings of the systematic review, document analysis, and qualitative interviews were presented in Chapters 02, 04, and 05, with an integration of the data in Chapter 06. The research identifies a significant gap between licensing and reimbursement, as well as the factors that impact this gap. It suggests ways to reduce this gap and highlights the variability in HTA recommendations and reimbursement across countries in the UK. The research explores the key drivers that play a role in this variability and suggests ways to reduce it. The study also highlights challenges in accessing medicines in the UK.

This research aims to stimulate stakeholders across the UK to address access to medicines challenges, take advantage of opportunities, implement new initiatives, and work together to find solutions. It provides useful background information and prompts interesting questions for future research in this area.
Acknowledgements

I would like to express my gratitude to my principal supervisor Professor Zaheer-Ud-Din Babar for allowing me to undertake this research and for his continued support, guidance, and encouragement. I am indebted to him for believing in me during my PhD and encouraging me to follow my passions and priorities. I am also grateful to my co-supervisor Dr. Syed Shahzad Hasan for the feedback and unwavering support.

In addition, I would like to thank the pharmaceutical industry experts who participated in the survey and semi-structured interviews for their time and valuable contributions.

I would like to dedicate this thesis to my family for their unwavering love and encouragement, as well as for inspiring me to pursue my dreams and goals.
External Outputs

Chapter 02 in this thesis contains material that has been published in peer-reviewed journal.

A further publication is being drafted from the thesis.

The author of this thesis was the first author for the mentioned below publications.

Publications were written solely (100%) by the first author and input from the supervisor’s (co-authors) was limited to the kind of guidance and feedback. Questions raised by journal editors, peer-reviewers, or copy editors were addressed by the author and approved by the supervisory team prior to publication.

1. **Access to medicines-a systematic review of the literature**
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   Status: Published
   The chapter 02 in this thesis contain this published systematic review of literature

2. **Access to medicines in the United Kingdom: A review of HTA recommendations for new medicines**
   Abstract accepted for poster presentation at ISPOR Europe 2020
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   Status: Published

3. **Marketing authorization of COVID-19 vaccines across UK, EU, and the US: fact-checking and the implications for future research**
   Abbas, N., Babar, ZUD. Journal of Pharmaceutical Policy and Practice
   DOI: [https://doi.org/10.1186/s40545-021-00400-0](https://doi.org/10.1186/s40545-021-00400-0)
   Status: Published

The author of this thesis was not the first author but was a contributor to the following book chapter on pharmacy practice research, definitions, theories, and model.

4. **Book Chapter:” Pharmacy Practice and its Research: Evolution and Definitions”**
   Status: Published.
The link to the in-press chapter is included below.
https://elsevierbook.proofcentral.com/authorproofs/1085f3535fc8f219cfeb7ebe37ef1ef0
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# Table of Contents

Chapter 1: Introduction .........................................................................................................................17

1.1. What is Access to Medicines? ............................................................................................... 17

1.2. United Kingdom’s Healthcare System ................................................................................... 20

1.3. Medicines in the UK Healthcare System ............................................................................... 24

1.4. Access to medicines in the UK ............................................................................................... 25

1.5. Rational of the Research Project ........................................................................................... 27

1.6. Aims and objectives ............................................................................................................... 28

1.7. Structure of the thesis ................................................................................................................. 29

Chapter 2: Systematic review of the literature on access to medicines in the UK context .................32

2.1. Introduction ................................................................................................................................. 32

2.2. Methods ...................................................................................................................................... 34

2.2.1. Scope of review: Inclusion and Exclusion Criteria ................................................................. 34

2.2.2. Search strategy ....................................................................................................................... 35

2.2.3. Data extraction and synthesis .............................................................................................. 36

2.2.4. Evaluation of quality and risk of bias in included studies .................................................... 37

2.3. Results ......................................................................................................................................... 37

2.3.1. Access to Medicines in the United Kingdom and Europe .................................................... 40

2.3.2. Health Technology Assessment (HTA) in Europe and the United Kingdom ......................... 41

2.3.3. Influencing factors for HTA recommendation ....................................................................... 42

2.3.4. Impact of HTA recommendations on budget, usage and cost effectiveness ......................... 42

2.3.5. Comparison of assessment practices, processes, and standards .......................................... 43

2.3.6. Study framework for HTA recommendations ....................................................................... 47

2.3.7. Comparison of UK and European HTA recommendations ................................................... 47
6.1.5 Objective 5: Medicine uptake post-licensing and/or health technology assessment recommendation ......................................................................................................................... 235

6.1.6 Objective 6: key challenges or barriers for access to medicines situation in UK. .......................................................... 251

6.2 Study Limitations ........................................................................................................................................................................... 263

6.3 Conclusion .......................................................................................................................................................................................... 263

6.4 Future research ................................................................................................................................................................................... 266

References ........................................................................................................................................................................................................... 269

Appendix 1: Search Terms and number of Search Results (‘Hits’) by Database or Journal .................. 289

Appendix 2: Summary of studies reported access to medicines in the UK and EU region. ............... 292

Appendix 3: Supplementary Material-Quality Assessment Table .................................................................................................... 352

Appendix 4: European Medicines Agency (EMA) approved list of innovative medicines licensed in 2017 ....................................................................................................................................................................................... 359

Appendix 5: Communication to identify and select expert for interview ........................................ 375

Appendix 6: Email invitation to identified expert referred by colleague or friend to participate in telephone interview ........................................................................................................................................... 377

Appendix 7: Email invitation to identified expert to participate in telephone interview ................. 379

Appendix 8: Semi-structured interview guide ......................................................................................... 380

Appendix 9: Participant Information Sheet ............................................................................................. 385

Appendix 10: Participant Consent Form ................................................................................................. 389

Appendix 11: Fisher’s Exact Test Result for Table 05 ............................................................................. 391

List of Tables

Table 1: The role of government and the NHS in planning and commissioning healthcare in the United Kingdom’s constituent countries (Source: (Anderson, Pitchforth, et al. 2022)) .............................................................. 22

Table 2: Pros and Cons of documentary analysis and expert interviews .................................................... 85

Table 3: Sources of Information for Document Analysis ........................................................................... 88

Table 4: Themes and questions covered in the final interview guide ........................................................ 96

Table 5: HTA assessment status of Selected Innovative Medicines in the United Kingdom .............. 114

Table 6: HTA Assessment status of Orphan VS Non-Orphan medicines in the United Kingdom........ 117
Table 7: HTA Assessment Status of Oncology VS Non-Oncology medicines in the United Kingdom .119
Table 8: Time from Medicines License Approval to HTA recommendation in the UK ..........121
Table 9: Participants Characteristics .................................................................................127
Table 10: Thematic Structure ............................................................................................130
Table 11: Suggestions to reduce the time lag between licensing and reimbursement ........228

List of Figures

Figure 1: Key milestones in Journey of New medicines from R&D to Patients Access ........19
Figure 2: Overview of the Research ..................................................................................31
Figure 3: Study selection process (PRISMA) ....................................................................39
Figure 4: Relationship between research philosophy and methodology (Source: Winit-Watjana 2016) .........................................................................................................................74
Figure 5: What is the purpose of mixing the methods (Source: Warfa 2016) ......................79
Figure 6: (Adapted from Source: Creswell and Clark 2007) ................................................80
Figure 7: Overview of the Research ..................................................................................82
Figure 8: Thematic Map .....................................................................................................135
Figure 9: Needs of Key Stakeholders ...............................................................................215
Figure 10: Factors likely to increase gap between licensing and reimbursement of medicines ....217
Figure 11: Schematic of routes to commissioning of new medicines in the NHS England ....219
Figure 12: Key Milestones from development to Access to Medicines ...............................223
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABPI</td>
<td>Association of the British Pharmaceutical Industry</td>
</tr>
<tr>
<td>AHSN</td>
<td>Academic Health Science Network</td>
</tr>
<tr>
<td>AWMSG</td>
<td>All-Wales Medicines Strategy Group</td>
</tr>
<tr>
<td>CCG</td>
<td>Clinical Commissioning Group</td>
</tr>
<tr>
<td>CDF</td>
<td>cancer drug fund</td>
</tr>
<tr>
<td>CER</td>
<td>Comparative Effectiveness Research</td>
</tr>
<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
</tr>
<tr>
<td>CRS</td>
<td>Conditional Reimbursement Schemes</td>
</tr>
<tr>
<td>DHPSS</td>
<td>Department of Health, Social Services and Public Safety</td>
</tr>
<tr>
<td>EAMS</td>
<td>Early Access To Medicines Scheme</td>
</tr>
<tr>
<td>EFPIA</td>
<td>European Federation of Pharmaceutical Industries and Associations</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>EUnetHTA</td>
<td>Joint Action European network for Health Technology Assessment</td>
</tr>
<tr>
<td>GB</td>
<td>Great Britain</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>Human Immunodeficiency Virus / Acquired Immunodeficiency Syndrome</td>
</tr>
<tr>
<td>HTA</td>
<td>Health technology assessment</td>
</tr>
<tr>
<td>ICC</td>
<td>Integrated care system</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental cost-effectiveness ratio</td>
</tr>
<tr>
<td>IFR</td>
<td>Individual Funding Request</td>
</tr>
<tr>
<td>ILAP</td>
<td>Innovative Licensing and Access Pathway</td>
</tr>
<tr>
<td>IMF</td>
<td>Innovative Medicine Fund</td>
</tr>
<tr>
<td>IPFR</td>
<td>Individual Patient Funding Request</td>
</tr>
<tr>
<td>IPTR</td>
<td>Individual Patient Treatment Request</td>
</tr>
<tr>
<td>MA</td>
<td>marketing authorization</td>
</tr>
</tbody>
</table>
MHRA: Medicines and Healthcare products Regulatory Authority
NHS: National Health Service
NI: Northern Ireland
NICE: National Institute for Health and Care Excellence
NOS: Newcastle-Ottawa Scale
OECD: Organisation for Economic Cooperation and Development
PAS: Patient Access Scheme
Patient W.A.I.T: Patient Waiting to Access Innovative Therapies
PCT: Primary Care Trust
P-SUB: Payer Strategy and Uncertainty Burden
QALY: Quality-Adjusted Life Year
RCT: randomized controlled trials
REA: Relative Effectiveness Assessment
RWE: Real World Evidence
SLR: systematic literature review
SMC: Scottish Medicines Consortium
UHC: Universal Health Coverage
UK: United Kingdom
VBP: Value-Based Drug Pricing
VPAS: Voluntary Scheme for Branded Medicines Pricing and Access
WHO: World Health Organization
Glossary and Definitions

Innovative medicine is a drug that has a new active ingredient or a new combination of active ingredients that has never been approved before (European Medicines Agency n.d.).

Orphan drugs are medicines or vaccines made to treat, prevent, or figure out what's wrong with a rare disease. The European Union (EU) defines a rare disease as a condition that affects no more than 5 out of every 10,000 people and either threatens their lives or makes them sick for a long time (Gammie, Lu, and Ud-Din Babar 2015).

National Health Service: Medical and health care services paid for by the UK government

The National Institute for Health and Care Excellence (NICE) is a group that works to improve health and social care on a national level by giving advice and guidance. NICE is an executive public body that is not part of a government department. It is funded by the Department of Health and Social Care.

The Scottish Medicines Consortium (SMC) is an independent body that works on its own. It tells the NHS Health Boards in Scotland what to do about medicines.

The All-Wales Medicines Strategy Group (AWMSG) gives advice to the Welsh Government about how medicines are used, how they are managed, and how they are prescribed.

The Department of Health, Social Services, and Public Safety (DHSSPS) helps the people of Northern Ireland improve their health and social well-being.

The Medicines and Healthcare products Regulatory Agency (MHRA) is in charge of regulating medicines, medical devices, and blood components for transfusion in the UK.
The European Union (EU) has an agency called the European Medicines Agency (EMA) that is in charge of evaluating and keeping an eye on medicines.

In cost-effectiveness analysis, the incremental cost-effectiveness ratio (ICER) is a number that sums up how cost-effective a health care is.

The Quality Adjusted Life Year (QALY) is a measure of disease burden that considers both the length and the quality of life. One QALY is equal to one year of life lived in perfect health. QALYs are calculated by figuring out how many years of life a patient has left after a certain treatment or intervention and giving each year a score based on how good it is (on a scale of 0 to 1).

Approval: When a regulatory authority gives a licence to a new active substance.

Company or Sponsor: The person or company that owns the product and started the submission process.

A comparator is a drug or placebo that is used as a standard in clinical trials and HTA reviews.

Economic Value (EV) is the process of figuring out how much a new therapy will cost and how much it will help or hurt the budget.

Health technology can include a wide range of treatments (drugs, medical devices, vaccines, and surgical procedures) as well as ways to stay healthy and avoid getting sick.
Health Technology Assessment (HTA) is a process that looks at the clinical benefit and cost-effectiveness of a health technology in the right setting. It also looks at the social and ethical effects of the technology if they are important.

Indication: The specific disease or condition that the medicine's active ingredient is meant to cure, relieve, treat, prevent, or diagnose.

Payer: Someone or something other than the patient who pays for the costs of medicines and/or health care.

Pharmacoeconomics is a field of science that compares the costs and benefits of different medicines.

Refers to a Health Technology Assessment Agency's recommendation that something is good. The recommendation could include restrictions on prescribing, like conditional clinical criteria, or it might not.

Risk is the chance that a medicine or treatment will hurt or make things worse.

Marketing Authorization: The legal permission that a national or regional regulatory authority gives to a company or sponsor to sell a medicine in the right market or region.

New Active Substance: A chemical, biological, biotechnology, or radiopharmaceutical substance that hasn't been used to treat people before and is going to be sold only with a prescription. It will be used to cure, relieve, treat, prevent, or diagnose diseases in people while they're still alive.
Patients' Access: This is how easy it is for patients to get the new medicine from public or private providers.

Reimbursement is when someone other than the patient pays for the cost of medicine or health care.
Chapter 1: Introduction

1.1. What is Access to Medicines?

Medicines are an important part of the overall healthcare system and a major tool to prevent and treating diseases and improve quality of life. As a result, access to medicines is regarded as a fundamental human right (Statement and Counterfeit 1998). Despite an increased international recognition of the necessity of ensuring access to medicines and a variety of international programmes and financial aid focused on enhancing medicines access, substantial inequalities in regular access to medications exist across and within nations (Forman and Kohler 2012). Better health outcomes and wider benefits to public health can be achieved if medicines are readily available, at reasonable prices, and affordable to individuals and healthcare systems. The World Health Organization (WHO) identifies inadequate access to healthcare as a major barrier to improving global health (WHO 2017).

Access to medicines has been defined as "having medicines continuously available and affordable in public and private health facilities or pharmacies that are within one hour's walk for the public" (Erginel 2014). Access to medicines is a complex and multidimensional subject and is defined by the WHO and the Management Sciences for Health (MSH) as "medicine’s availability, affordability, accessibility, and acceptability to the patient, with cross-cutting dimensions relating to the quality of both medicinal products and pharmaceutical services" The World Health Organization defines access to medicines using two key dimensions: One is availability, which refers to the degree to which new medicines
are available in the intended market. The second is affordability, which refers to the degree to which the prices of medicines are in line with the purchasing capacity of healthcare systems and/or patients (WHO 2010). The availability of medicines is mainly dependent on licencing approvals and subsequent reimbursement recommendations at the national, regional, or local level (“Briefing paper : Who decides the price and availability of NHS medicines ” 2019).

Access to medicines is a growing concern globally. The World Health Organization (WHO) strives for access to medicines at the global level. Access to medicines affects people from all socioeconomic backgrounds. "It is not confined to underdeveloped or developing countries or certain diseases, but the issue has emerged as a global challenge impacting people all over the world" (Vink 2018). Although countries in the European Union (EU) pledge to achieve targets for Universal Health Coverage (UHC) set out by WHO in 2015, people with low levels of income in these countries are pushed further into poverty due to out-of-pocket health expenditures (WHO 2019). Resource limitations, increased cost of medicines, and ageing population are also some of the key factors that have an impact on access to medicines worldwide (Ranson et al.2019).

There is no point in making new medicines if people who need them can't get them. Once a new treatment has been researched and developed for an average of ten years, there are three more steps that must be taken before it can be administered to patients. First, marketing authorization must be given, which shows that the therapy is good, safe, and effective. After the marketing authorization is approved, the authorities in each country have to decide on market access, which means whether or not the therapy will be covered by the
national reimbursement programme or through any interim arrangement. This is done so that all patients can afford the intervention. As these are public health care costs, reimbursement decisions for new medicines need to be made in a way that is clear and based on facts. England and Scotland make decisions about reimbursement in different ways, leading to great differences in how patients can receive care in the UK. Once innovations are reimbursed, patient access must be achieved. This means that the patients for whom medicines are meant must be able to use them after a specialist prescribes them, according to their marketing authorization, reimbursement recommendations, and the latest scientific guidelines. Innovative medicines go through four key stages before reaching patients. The following key milestones must be reached for innovative medicines to reach patients (Collins 2019; Jansen and Amesz 2020). After the approval of a medicine's marketing authorization, gaining access to the market and patients are two major significant milestones that we are focusing on for this Ph.D. thesis. In addition, this research work is focused on new and innovative medicines. Generic or biosimilar medicines were considered outside the scope of this research.

Figure 1: Key Milestones in the Journey of New Medicines from R&D to Patients Access
(Adopted from Source: Jansen and Amesz 2020)
1.2. United Kingdom’s Healthcare System

In the United Kingdom, all permanent residents (around 58 million) have access to the public healthcare system. Healthcare is provided free to all and it is funded by taxation. Around 18% of income tax is allocated towards healthcare. The UK’s healthcare spending is approximately 8.4 percent of the gross domestic product, i.e., £ 0.18984 trillion. In 2021, the United Kingdom spent $5,387 per person on healthcare,, placing it fourteenth among Organization for Economic Cooperation and Development (OECD) countries. In terms of healthcare expenditure as a share of GDP, the UK ranks fifth among OECD countries (OECD Data 2021). Although the healthcare system is largely public, the private healthcare sector is also growing, although it is very small. In the United Kingdom, the government contributes 85% of healthcare expenditures, with the remaining 15% coming from the private sector (Chang et al., 2010). The responsibility for health services is delegated to the Scottish, Welsh, and Northern Ireland governments. Each government has control over the amount of spending, governance, and structure of the NHS. Healthcare expenditures per capita in 2018–2019 were reported to be highest in Northern Ireland (2,436 pounds per person), while the lowest were in England (2,269 pounds per head) (Parliament. House of Commons 2019). The National Health Service (NHS) is the publicly funded healthcare system, and with 1.3 million employees, it is one of the largest employers in the UK (Grosios et al. 2010).

Since the late 1990s, England, Scotland, Wales, and Northern Ireland have been responsible for health care. The UK government allocates a specific budget for health care in England, but Scotland, Wales, and Northern Ireland get a general block grant for public spending. Locally, clinical commissioning groups (CCGs) in England (to be replaced by integrated care systems (ICS) by 2022), health boards in Scotland and Wales, and the health and social care
board in Northern Ireland plan health and care services. Local companies implement national plans or strategies, such as the NHS Long-Term Plan in England, the National Performance Framework in Scotland, A Healthier Wales: long-term plan for health and social care in Wales, and Commissioning Plan Directions in Northern Ireland (Anderson, et al. 2022). Each individual country in the UK has its own planning framework with distinct national and local functions for the respective government and the NHS, as shown in the table below.
Table 1: The role of the government and the NHS in planning and commissioning healthcare in the constituent countries (Source: (Anderson et al. 2022))

<table>
<thead>
<tr>
<th>Role of government</th>
<th>England</th>
<th>Scotland</th>
<th>Wales</th>
<th>Northern Ireland</th>
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<tbody>
<tr>
<td>DHSC issues the “NHS Mandate” annually, which sets out objectives and requirements of the NHS and sets the budget.</td>
<td>The Scottish Government determines the resources allocated to the NHS in Scotland and sets its strategic direction and delivery priorities.</td>
<td>The Minister for Health and Social Services sets the overall policy context and direction for the NHS through national strategies and delivery plans. In partnership with NHS Wales, the government sets out an “NHS Wales Planning Framework” and a National Clinical Framework.</td>
<td>Minister of Health’s priorities and targets for health and social care are set out annually in the “Commissioning Plan Directions”.</td>
<td></td>
</tr>
<tr>
<td>Role of the NHS</td>
<td>NHS England sets strategic direction and overall commissioning strategy, currently through “The NHS Long Term Plan”.</td>
<td>Planning and delivery responsibilities are devolved to 14 territorial NHS Boards, seven National Boards and one public health body (Public Health Scotland).</td>
<td>Planning and delivery responsibilities are devolved to seven Local Health Boards (LHBs) and three NHS trusts: public health, ambulance and specialist cancer services.</td>
<td>The Health and Social Care (HSC) Board and the Public Health Agency are required to respond to the “Direction” by producing an annual “Commissioning Plan”.</td>
</tr>
<tr>
<td>Accountability of the NHS to the parliament/government</td>
<td>The Chief Executive of NHS England is accountable to the DHSC and the parliament on the basis of objectives, goals and deliverables.</td>
<td>The Scottish Government measures performance against Local Delivery Plan Standards, which are priorities set and agreed between the Scottish Government and NHS Boards.</td>
<td>LHBs are accountable to the Minister for Health and Social Services. The Welsh Government monitors and reviews Integrated Medium-Term Plans and performance against quality.</td>
<td>Progress of the HSC Board is monitored according to a set of core performance indicators, the “Indicators of Performance Direction”, set alongside the “Commissioning Plan Directions”.</td>
</tr>
<tr>
<td>England</td>
<td>Scotland</td>
<td>Wales</td>
<td>Northern Ireland</td>
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<tr>
<td>specified in the NHS Mandate and the NHS Outcomes Framework.</td>
<td></td>
<td>indicators contained in the National Clinical Framework.</td>
<td></td>
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</tr>
<tr>
<td><strong>Planning/Commissioning at national level</strong></td>
<td>NHS England directly commissions specialised services (e.g. secure mental health care), military and veteran health services, health services for people in prisons and some public health functions.</td>
<td>The National Planning Board in Scotland is used by NHS Boards and the Scottish Government Health and Social Care Directorates to jointly plan services on a national level. National and Specialist services are commissioned by NHS National Services Scotland’s National Services Division.</td>
<td>The HSC Board commissions care and manages the performance of five geographic Health and Social Care Trusts, the Ambulance Trust and primary care organisations working with five Local Commissioning Groups.</td>
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<tr>
<td><strong>Planning/Commissioning and at local level</strong></td>
<td>Clinical Commissioning Groups (CCGs) are responsible for commissioning services for their local populations. Around 60% of the budget is devolved to CCGs. CCGs will be replaced by Integrated Care Systems in July 2022.</td>
<td>NHS Boards produce annual Delivery Plans aligned with government priorities and objectives. This process is under review. The Scottish Government is working towards commissioning 3-year operational plans from 2022/2023. NHS Boards also work with Local Authorities as part of Integration Joint Boards to achieve health and well-being objectives through strategic joint commissioning plans.</td>
<td>Local Commissioning Groups assess the needs of the population and identify priorities for both health and social care services. They can secure services to meet that need from any appropriate provider, although Health and Social Care Trusts are the main provider.</td>
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<td></td>
<td>LHBs and NHS trusts produce Integrated Medium-Term Plans guided by the NHS Wales National Planning Framework, updated annually. LHBs also partner with local authorities as part of Regional Partnership Boards and Public Service Boards that produce integrated plans to achieve health and well-being objectives.</td>
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</table>
1.3. Medicines in the UK Healthcare System

Medicines, which are an important component of the healthcare system, have a critical role in protecting, maintaining, and restoring people's health. Therefore, the availability of suitable, high-quality medications in sufficient quantity and at reasonable costs is a top concern.

The UK is a major producer of pharmaceuticals. The pharmaceutical industry contributes approximately £14 billion to the economy and employs approximately 60 000 people (ABPI 2021). Patients are not charged for medicines they take while in the hospital. However, patients in England pay £9.15 per item for prescriptions filled out in the community (NHS England 2020). Exemptions apply to a wide range of people, including those under 16 and over 60, those with low incomes, pregnant women, and people with long-term illnesses such as diabetes or epilepsy. As a result, about 90% of all prescriptions are given for free (NHS England, 2020). Wales got rid of prescription fees in 2007, Scotland did the same in 2011, and Northern Ireland did the same in 2010 (Kulakiewicz et al. 2022).

Medicines are allocated around £20 billion from the healthcare budget in the UK (England spends £16.8 billion, Scotland spends £1.7 billion, and Wales spends £800 million). The UK spends 11.76% of its healthcare expenditure on medicines and is ranked 26th compared to other OECD countries. The United Kingdom spends $590 per person on medicines, placing it eighteenth among OECD countries (OECD data 2021). To ensure the success of a healthcare system in any country, patients must have access to medicines (Royal Pharmaceuticals Society, 2016). According to data gathered by the patients, W.A.I.T. Indicator survey, the average wait time for patients to gain access to therapies in EU and EEA countries remains anywhere from 504 to more than 883 days. An analysis of the core causes of these
challenges demonstrates they are multi-factorial, including late starts of market access assessments, duplicative proof requirements, national pricing and reimbursement rules, as well as company decisions motivated by a mix of these variables (EFPIA 2021). When compared to other EU countries, the UK is said to be lagging behind in terms of access to newer medicines (ABPI n.d.).

1.4. Access to medicines in the UK

Timely access to medicines is an essential component of a healthcare system. The timeliness of access to medicines primarily relies on three stakeholders: the pharmaceutical industry as a developer of new medicines; the regulators, as licencing bodies; and the health technology assessment bodies or payers, liable for evaluating whether a new medicine offers better value for money and/or reimbursing the expenses of the medicines (Baird et al. 2014).

The regulatory body for the licencing of medicines in the UK is the Medicines and Healthcare Products Regulatory Authority (MHRA). Before Brexit, the European Medicines Agency (EMA) was another regulatory body for the licencing of medicines in EU countries, including the UK. Before a medicine is considered for a license, it will typically have undergone 12 years of research and development. The purpose of the licencing process is to consider whether the medicine has a measurable effect against a comparator in a clinical trial (referred to as "efficacy") and, in general, whether it is likely to have an acceptable level of safety and quality. The Medicines and Healthcare Products Regulatory Agency (MHRA) has published guidance on eight new routes, including six national routes and two international routes, by which a manufacturer can apply for a licence to market a medicine in the UK since leaving the EMA Centralised Authorization Procedure. Most items will likely go
through national routes for review, where the process can take anywhere from 67 to 150 days depending on factors including the complexity of the application, the degree of innovation involved, and whether or not the product is already on the market in another country (Matar et al. 2021).

Once the medicines are licenced for human use, the prescribers can use the newly licenced medicines. However, for the wider use of these medicines, prescribers and the NHS have to wait for official guidance. The NHS receives this guidance from various health technology assessment bodies across UK licensed medicines. However, for the wider use of these medicines prescribers and NHS have to wait for the official guidance. The NHS receives this guidance from various health technology assessment bodies throughout the UK.

The National Institute for Health and Care Excellence (NICE) in England provides guidance on the use of new and currently available medicines. The Wales All-Wales Medicines Strategy Group (AWMSG) makes recommendations for the NHS in Wales. However, AWMSG in Wales accepts the NICE guidance and medicine is not reviewed by AWMSG if NICE considers evaluating it in the next 12 months. Northern Ireland accepts guidance issued by NICE or SMC, and it adopts a recommendation shortly after the recommendation is available from NICE or SMC. The Scottish Medicines Consortium (SMC) provides advice to NHS Scotland on new drug therapies and is not reliant on NICE (Payne 2012). Health technology assessment (HTA) is used as a tool by the above-mentioned health technology assessment bodies to provide guidance for pricing and reimbursement recommendation.

Health technology evaluation is frequently used in the UK to determine reimbursement status and net price, further illustrating the linked nature of the pricing and reimbursement systems in the country. Drug prices are evaluated by NICE, but the NHS controls the purse
strings and often negotiates lower prices. After receiving the marketing authorization, the holder may charge whatever price they see fit for the pharmaceutical. The Voluntary Scheme for Branded Medications Pricing and Access ("Voluntary Scheme"); and the so-called "Statutory Scheme" manage the prices of new medicines after they have received marketing authorization. Those who do not take part in the Voluntary Scheme but nevertheless supply the NHS with brand-name medications will be held to the requirements of the so-called "Statutory Scheme." Price and profit control under the current voluntary scheme, which went into force on January 1, 2019, is highly intricate. By default, the "Statutory Scheme" applies to the new medicines that do not take part in the NHS Voluntary Scheme. Marketing authorisation holders participating in this programme will be required to make quarterly payments to the NHS based on their net sales of branded items. Some form of price control is also built into this plan. Drug prices in the UK are affected by a variety of factors, including governmental and healthcare system regulations, commercial arrangements between pharmaceutical companies and the NHS, and market competition. Keep in mind that the UK list price is frequently used as a standard by nations with reference pricing systems. Companies may find this to be a compelling argument in favour of entering into arrangements with the NHS that allow for price reductions without impacting the reference price. (Hull et al. 2020).

1.5 Rational of the Research Project

Several studies have looked at various aspects of this topic, ie, access to medicines in the United Kingdom. Although some anecdotal evidence was available, a thorough and detailed review of the literature on access to medicines within the UK was lacking, and a systematic review of the literature was needed to fill this gap. As a result, in this PhD research, as a first
step, a systematic review has been carried out in this context. The objective of a systematic review of the literature is to critically review original research papers and explore the topic in detail. The systematic review included research papers on access, availability, funding, HTA, and legislation of medications. Furthermore, this review identifies gaps in the available literature and makes recommendations for further research.

Information on the overall aim and objectives of the Ph.D. project is presented below. These objectives were derived from the previously mentioned systematic review of the literature (Abbas et al. 2019), which is presented in Chapter 2 of the thesis. This is grounded in a systematic review that screens many studies that portray information, problems, and empirical research conducted on access to medicines in the UK context. The countries of the European Union, including the UK, incur a large part of their healthcare expenditures on medicines. Hence, it is important to evaluate the access to medicine situation in the UK, the factors that impact access to medicine, and the issues related to reimbursement and funding of medicines.

1.6 Aims and objectives

Aims:
To evaluate the access to medicine situation in the UK (England, Scotland, Wales, and Northern Ireland).

Objectives:

- To conduct a systematic review of the literature to critically review and analyse the original research on access to medicines in the UK.
- To study the gap between licencing and health technology assessment recommendations on treatment availability for new innovative medicines in the UK.
- To study timelines from licensure to reimbursement of medicines
- To study differences and variability in health technology assessment recommendations across countries in the UK.
- To study medicine uptake post-licensing and/or health technology assessment recommendations
- To identify key challenges or barriers for access to medicines in the UK.

1.7 Structure of the thesis

Chapter 01: This is the introductory chapter, which discusses the definition of access to medicines, the UK healthcare system, medicines in the UK healthcare system, and access to medicines in the UK. The rationale of the Ph.D. research, aim and objectives of the thesis and the overall structure of the thesis.

Chapter 02: This chapter includes a systematic review of the literature on access to medicines in the UK context, which was published in a peer-reviewed journal (Abbas et al. 2019). The objectives of the research in this thesis have come from this systematic review of the literature.

Chapter 03: This chapter describes the methodology and methods adopted by this research project to achieve the specified goals and objectives. This chapter will first go over how to choose a research philosophy, then the research design, as well as the benefits and drawbacks of the various research methods. This will be accompanied by a discussion of their ability to generate valid results that meet the thesis goals and objectives. The sample size and sampling strategy, as well as the data analysis techniques used, are discussed in this chapter.

Chapter 04: This chapter presents findings from document analysis of licencing and health technology assessment recommendations for new innovative medicines in the United Kingdom. The sample included 56 new innovative medicines licenced by the European Medicines Agency (EMA) in 2017 and their subsequent assessments by health technology assessment (HTA) bodies in the United Kingdom (UK) from the date of licencing of the medicines in 2017 until January 2020.

Chapter 05: This chapter presents the findings of a qualitative study exploring the situation of access to medicine in the United Kingdom.
Chapter 06: This chapter includes a general discussion on research results, study limitations, future work, overall conclusions, and recommendations. The results and findings of both the document analysis (Chapter 04) and qualitative interviews (Chapter 05) are discussed in the context of the wider literature and the research objectives. Where possible, the findings of both the document analysis and the qualitative interviews are integrated to facilitate a better understanding of the results in Chapter 6. This integration of data was done by condensing the findings from different methods, comparing and contrasting the quantitative and qualitative results where needed, and just talking about how their conclusions could be expanded.

An overview of the thesis research, including the studies performed and a systematic review of the literature, is shown in Figure 2.
Figure 2: Overview of Research

Aim
To Evaluate Access to Medicines Situation in the UK

Objective 1
To conduct SR of Literature to critically review and analyse the original research on access to medicines in UK.

Objective 2
To study gap between licencing and health technology assessment

Objective 3
To study timelines from licencing to reimbursement of medicines

Objective 4
To study differences/variability in health technology assessment recommendation across countries in UK.

Objective 5
To study medicine uptake post-licencing and/or health technology assessment recommendation

Objective 6
To identify key challenges or barriers for access to medicines situation in the UK.

Research Activities

CHAPTER 02
Systematic Review of Literature on access to medicines in the UK context

CHAPTER 04
Study 1: Document Analysis of Licensing and HTA Recommendations for new innovative medicines across the UK

CHAPTER 05
Study 2: A qualitative study exploring access to medicines situation in the UK

CHAPTER 06
General Discussions, Study limitation, future work, Overall

Associated Objectives

Objective 1

Objectives 2,3&4

Objectives 2,3,4,5 & 6

Objective 6
Chapter 2: Systematic review of the literature on access to medicines in the UK context.

This chapter expands on the preceding chapter by presenting a systematic review of the literature on access to medicines in the United Kingdom. This chapter presents the complete systematic review, which was published by author of this thesis in a peer-reviewed journal (Abbas et al. 2019). This systematic review of the literature informed the research objectives of this thesis.

2.1 Introduction

Access to medicines is tied to the availability of medicines as well as a person's financial and physical ability to get and use them. This is an important part of getting the best possible health (Babar et al. 2018)(WHO 2010).

Access to medicines is a problem all over the world, not just in poor countries or for people with diseases that do not receive enough attention (World Economic Forum 2016). About one-third of the world's people don't have access to medicines they need (WHO 2002). Even though developed places like Europe say they work toward WHO goals for universal health coverage, people with lower incomes are 5 times more likely to see access as a barrier (Cylus and Papanicolas 2015).

Access to medicines is affected by a number of things. Budgetary constraints, rising costs, and an ageing population are some of the biggest problems (Ranson and Llp 2019). The rising cost of medicines around the world could make it harder for people to get the medicines they need (Nicod and Kanavos 2012).
The healthcare system in the United Kingdom (UK) is primarily a public system, with taxation accounting for 80% of its funding, national insurance accounting for 12%, other levies and miscellaneous accounting for 4%, Trust interest receipts accounting for 3%, and capital receipts accounting for 1%. In contrast to the United States, the level of private insurance coverage in the UK is relatively low. The importance of the private healthcare sector in the United Kingdom is growing (Mossialos et al. 2002). Prescribers in the National Health Service (NHS) will be able to use the medicine after it has been approved in the United Kingdom, although the NHS and prescribers may choose to wait for official instructions on its usage. The goals of this guide are distinct from those of licensing, which are focused on safety and effectiveness. Although the NHS recommendations do investigate the medicine's efficacy, they also reflect its clinical and cost effectiveness. Guidelines for the use of medicines in the NHS are produced by a number of different organisations in the United Kingdom. These include the National Institute for Health and Clinical Excellence (NICE), the All Wales Medicines Strategy Group (AWMSG), the Scottish Medicines Consortium (SMC), and the Department of Health, Social Services, and Public Safety in Northern Ireland (Payne 2012).

One-eighth of the world's most often prescribed drugs were created in the United Kingdom (UK), making it a global leader in the life sciences industry (Clough 2015). But it has been said that the UK is slow compared to other EU countries when it comes to paying for new medicines (ABPI n.d.).

The access of medicine in the United Kingdom has been the subject of numerous studies. In a study the medicines appraisal process in Wales compared the procedures and recommendations with those of the other two Health Technology Assessment organisations in the United Kingdom (Varnava et al. 2018).
affects HTA recommendations in Scotland (Charokopou et al. 2015). A study by Bourke et al. (2018) looked at whether people in the UK like the way the NHS pays for treatments for rare diseases now. Examines how changes in prescription copayments have affected dispensing rates in Wales (Alam et al. 2018). In this systematic review are studies that compare the United Kingdom to others around the world.

Despite the availability of several research articles, there is currently no comprehensive and systematic evaluation of the existing literature on wider access to pharmaceuticals in the United Kingdom. In light of this, a review has been conducted. The purpose of this systematic review of the literature is to evaluate and evaluate critically the original research publications on the broader topic of access to medications in the UK (England, Wales, Scotland & Northern Ireland). The articles also cover access to medicines, availability of medicines, funding for medicines, the impact of HTA on access, and pharmaceuticals regulation. In addition, the study identifies literature gaps and makes suggestions for further research.

2.2 Methods

2.2.1 Scope of review: Inclusion and Exclusion Criteria

The concepts of Penchansky R. and Thomas J.W. (The notion of access: definition and relationship to customer satisfaction.) and the WHO’s access definition Australian National Medications Policy were used to build the theoretical framework for the research of access to medicines.

Availability, accessibility, acceptability, affordability, pricing, and reimbursement are all offered as components of the larger concept of access. This is the criterion by which the studies for this systematic review were chosen (Penchansky and Thomas 1981; Policy2000).
All studies that analyse access (perceived/actual) or examine any of the components that contribute to the concept of access are included in this review since they fit within the chosen framework.

As can be seen in Figure 3, the PRISMA principles have been strictly adhered to throughout this systematic study. The titles and abstracts of the primary articles were reviewed in light of an eligibility criterion.

Predetermined inclusion/exclusion criteria were created to reflect the aim of the review, and these were used to choose the articles. Full-text original research publications on access to medications focusing on the United Kingdom are eligible for inclusion, as are articles comparing the United Kingdom to other nations. The articles had to be written in English and published between January 1, 2008 and October 14, 2018. Original research publications and studies involving humans were the only kind of content considered in the search. Studies that did not fit the review criteria were disregarded after their titles and abstracts were read. The full texts of the remaining papers were ultimately analysed.

2.2.2 Search strategy

Scholarly articles published between January 1, 2008, and October 14, 2018, were found using a systematic search strategy for this review. The search technique was made with the purpose of being as inclusive as possible so that all relevant articles would be found. Journals such as BMJ, Lancet, Value in Health, Pharmacoeconomics, Pharmacoeconomics Open, Journal of Pharmaceutical Policy and Practise and Health Policy were searched for in addition to PubMed, Scopus, and Science Direct databases.
The search terms for the chosen databases and journals were combined and integrated. There were three different sets of words used. The searches were performed using "Boolean Operator" rules. The Boolean operator "AND" was employed to join the important terms. The Boolean OR operator was employed to avoid performing the same searches twice. The asterisk (*) was also used to increase the efficiency of the search. There was a combination of access OR availability OR affordability OR funding OR cost* OR price * OR reimbursement AND drugs OR medicine* OR pharmaceutical* AND United Kingdom OR UK OR England OR Wales OR Scotland OR Northern Ireland in the search criteria (title, abstract, text, keyword). Additional primary literature not uncovered by the initial search was located by examining the reference lists at the ends of the chosen articles. In Appendix 1, we detail our search strategy.

2.2.3 Data extraction and synthesis

The researcher next went through all the retrieved titles to determine which were relevant to the studies they had identified. As a result, we compiled all of the salient characteristics into a single extraction table. The researcher gathered the information and consulted with the supervisor about any discrepancies he found. Author names and publication years were culled, as were the study's aims and objectives, methodology, and results. Appendix 2 contains the extraction table.

Finding commonalities required a synthesis of the articles. The report dissected two categories of research: (a) studies focused solely on the United Kingdom, and (b) comparative studies. Due to the abundance of literature on the latter topic, it was incorporated into the results and synthesis, opening the door to a study of similarities and differences in medication access throughout Europe, including the United Kingdom.
2.2.4 Evaluation of quality and risk of bias in included studies

Each original article included in this review was rated by the researcher, and then the researcher and supervisor discussed their ratings to come to a consensus. For measuring bias in primary research papers, the modified Newcastle-Ottawa Scale (NOS) (Wells, et al. 1993) was chosen since it is user-friendly and accurate. Organizational characteristics (such as HTA or NHS), data sources (database or questionnaire-based), intervention descriptions (such as MEA), comparability (UK vs. EU), outcome assessments (such as QALY or preferences), and data presentation were all evaluated for each of the original articles chosen (e.g., percentage, median). The researcher used the Newcastle-Ottawa scale to evaluate each publication. Articles were deemed to be of "good quality" (5-6) on the Newcastle-Ottawa (NOS) scale if they received an overall score of 7. "good" (5-8 points) or "excellent" (5-7 points) (0-2 points). Quantitative analysis revealed that 44 of the articles were of high quality, while the remaining articles were rated only fair. Appendix 3 is a quality assessment table.

2.3 Results

The search identified a total of 20,097 titles (PubMed n = 4291, Scopus n = 6707, Science Direct n = 1363, additional records obtained from journals n = 7736). The screening process involved 1240 abstracts, after which irrelevant and duplicate records were removed. 1142 of these investigations were rejected as insufficient. 45 of the other 98 articles were ignored because they did not provide any information on access to medicines, did not provide any examples from the UK or focused on any other country. (Figure 3).

Only 17 of the 53 articles were about the UK. The other 36 were comparative studies of more than one country that included the UK. From the data taken from the 53 articles, key themes
were made. These themes were access to medicines, health technology assessment (HTA), pricing, health technology assessment, risk-sharing agreements, and the role of stakeholders in the reimbursement process and their thoughts on it. The following is the number of articles for each theme:

<table>
<thead>
<tr>
<th>Themes</th>
<th>Number of articles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access to Medicines</td>
<td>6</td>
</tr>
<tr>
<td>Health Technology Assessment</td>
<td>33</td>
</tr>
<tr>
<td>Patient Access Schemes, Managed Entry Agreements and Risk-Sharing Agreements</td>
<td>7</td>
</tr>
<tr>
<td>Pricing</td>
<td>2</td>
</tr>
<tr>
<td>Stakeholders’ involvement/ views on Reimbursement Process</td>
<td>3</td>
</tr>
</tbody>
</table>

When necessary, we added subthemes to the top-level categories of our themes. The data extracted from each study included in this review are included in Appendix 2.
Characteristics of the studies

20,097 Records identified through database searching

PubMed n=4291, Scopus n=6707, Science Direct n=1363, Additional records through Journals (BMJ (n=333), Lancet (n=2427), Value in Health (n=395), Pharmacoeconomics (n=2273), Pharmacoeconomics Open (n=106), (n=2273), Health Policy (n=1935), Journal of Pharmaceutical Policy and Practice (n=267)) n=7736

17,657 records excluded after titles search & duplicates removed

1240 abstracts screened

1142 Records excluded (not meeting the inclusion criteria)

98 Full-text articles assessed for eligibility

45 Full-text articles excluded with reasons
- review articles,
- non-UK setting,
- non access issue, etc.

53 Studies included in the literature review

Figure 3: Study selection process (PRISMA)
2.3.1 Access to Medicines in the United Kingdom and Europe

In terms of progress toward the World Health Organization's objective of Universal Health Coverage (UHC), Europe is one of the world's most developed regions. Access to pharmaceuticals varies widely within the European Union (Cylus and Papanicolas 2015). Several other factors, such as quality of care and the length of wait times for health care, may also have had a role in this barrier. Access to healthcare services, including medicines, has been found to be constrained by poor standards of care and lengthy waiting times. Generally speaking, these variables contribute to accessibility problems for patients of all income levels, but may become an affordability problem for low-income patients if they are forced to pay high out-of-pocket costs and seek care in the private sector. (Cylus and Papanicolas 2015)

Recommendations from reimbursement organisations can have a significant impact on patients' ability to obtain the necessary medications. Ragupathy et al. compared the number of medications authorised and supported in the United States, the United Kingdom, Australia and New Zealand, as well as the number of innovative medicines, were compared (Ragupathy et al. 2012). According to the study, the National Health Service (NHS) of the United Kingdom sponsored relatively more drugs, including the latest and most creative ones. A study reported that more people are covered by health insurance in Japan, and there are fewer obstacles for those seeking care there, compared to the populations of France, Germany, and the United Kingdom (UK) (Ragupathy et al., 2012). There was a 66-day lag in Japan between when a licence was granted and when reimbursement payments were made. On the other hand, in both Germany and the United Kingdom, this period was recorded as lasting 120 days.
There were no major disparities between medicine pricing in Japan and the chosen EU countries (Takayama and Narukawa 2017).

The time to the entry of new medications into the various European countries is one factor that contributes to the observed variation in access to medicines. A study by Ferrario (Ferrario 2018) examined the time it took for certain European Union (EU) countries to approve cancer drugs (Belgium, Estonia, Scotland, and Sweden). According to the results, the existence of a local manufacturer sales representative, pre-launch evidence of enhanced therapeutic value, and a shorter time gap since EU-wide marketing authorization all boosted the likelihood of early access to medicines. Initiating communication between pharmaceutical companies and regulatory bodies at an early stage could aid in the identification of medicines with the potential to have greater clinical value. Drug approval and market entry are slower in nations with smaller markets, such as Estonia (Ferrario 2018).

The high costs of medicines, the lack of evidence on efficacy and safety, and a societal preference for sponsoring orphan medicines all contribute to a lack of uniformity in patient access to medicines in Europe for the treatment of uncommon diseases. Among developed nations, Germany, Switzerland, and France spend the most money for treatments for rare diseases. More patients can receive treatments for uncommon diseases in comparatively shorter time in the United Kingdom, Germany, Switzerland, France, and Scandinavian countries (Detiček et al. 2018).

2.3.2 Health Technology Assessment (HTA) in Europe and the United Kingdom

Health technology assessment (HTA) has become a key part of making pricing and reimbursement recommendations, so it is now seen as a more immediate rather than a more
distant factor in determining access.

### 2.3.3 Influencing factors for HTA recommendation

According to an analysis of reviews by the All Wales Medicines Strategy Group (AWMSG), the quality of the RCT has a major effect on the HTA recommendations. According to Linley and Hughes (2012), this influence on recommendations can be explained by the fact that high-quality RCTs have a higher incremental cost-effectiveness ratio (ICER). Another study found that cost-effectiveness evaluations are taken into account heavily when making reimbursement recommendations for the Scottish Medicine Consortium (SMC) found that cost-effectiveness evaluations are taken into account heavily when making reimbursement recommendations for the Scottish Medicine Consortium (SMC) (Charokopou et al. 2014).

### 2.3.4 Impact of HTA recommendations on budget, usage and cost effectiveness

It is crucial to evaluate HTA recommendations in light of their effect on patient access. Neill and Devlin (2010) present a method for quantifying the extent to which patients face barriers to care as a result of various NICE (National Institute of Health and Care Excellence) recommendations, with a focus on the more stringent of these guidelines. Although these estimates of availability are not completely sound, they are an effective means of communicating HTA recommendations (Neill and Devlin 2010). Another study indicates a strong correlation between the magnitude of restrictive recommendations by NICE and the financial burden on the NHS (Mauskopf et al. 2013).

NICE’s HTA recommendations have been studied by E.S. (2009) (Dietrich 2009), and their findings suggest that negative and restricted HTA recommendations do not significantly affect the rate of prescriptions written or the cost of those prescriptions. This ineffectiveness may
result from prescribers' unwillingness to follow HTA's suggestions. Possible causes include recommendations makers in HTA boards and local health services having conflicting goals. Improving physician compliance with the HTA recommendations is essential for a significant reduction in prescription rates and costs (Dietrich 2009)(Schaffer et al. 2015).

The assumption that medicine prices go up in tandem with inflation is refuted. According to the findings, pharmaceuticals were evaluated as more economically viable than the previous results of the NICE assessment indicated. As a result, some previous negative or restricting outcomes of NICE recommendations may really have been the result of positive decisions (Hoyle 2008).

2.3.5 Comparison of assessment practises, processes, and standards

A study found that the eight European countries (France, Germany, England, Sweden, Italy, Netherlands, Poland, and Spain) evaluate the same kind of evidence when determining the value of new drugs. However, the criteria and endpoints that are actually used, the needed level of proof, and the manner in which they are integrated might vary widely from country to country. Differences in HTA suggestions and recommendations may be explained by incorporating social value judgements beyond clinical and economic evaluation. Improved transparency in the selection of evaluation criteria, their importance, and the intensity with which they are used may pave the way to more fair evidence-based recommendations. This has the potential to boost public confidence and fairness while also increasing the effectiveness with which resources are allocated (Angelis, Lange, and Kanavos 2018).

A study looked into the value of indirect comparisons in early benefit assessment of new pharmaceuticals in Germany and other HTA procedures in the United Kingdom, France, and
Scotland. When comparing efficacy, effectiveness, and safety, head-to-head studies are the gold standard. The study shows that it is difficult to make indirect comparisons between HTA bodies, and it is clear that the pharmaceutical industry has a hard time implementing them due to stringent standards (Lebioda et al. 2014).

When comparing HTA processes in Scotland and Poland, Kolasa and Wasiak (Kolasa and Wasiak 2012) found that the Polish HTA agency, Agencja Oceny Technologii Medycznych (AHTAPoL), makes more negative recommendations than the Scottish Medicines Consortium (SMC). The lack of cost effectiveness was a major factor in the negative recommendations in Scotland, while concerns about patient care and safety were the main reasons for negative recommendations in Poland. When AHTAPoL recommended against a practise, SMC was found to support it. Regarding clinical and economic evaluations, the study found that the Scottish HTA methodological guidelines provided greater information (Kolasa and Wasiak 2012).

According to a study, the French agency Haute Autorité de Santé (HAS) is more likely to recommend drugs than SMC. It is possible that variations in clinical guidelines and selection of comparators at the regional level account for some of the recommendations' variances. Manufacturer-set pricing and reimbursement present difficulties for SMC. Guidelines are based on clinical and monetary evidence. The CEPS (Comité économique des produits de santé) negotiates prices independently of the HAS reimbursement recommendation, which is based on clinical evidence. Manufacturers can benefit in different ways from the two techniques outlined above. A manufacturer in Scotland may have a relatively high price but a lower sales volume due to restricted use, while a French supplier may offer more sales in terms of volume at a lower price. The study descriptions of the differences between the
various sets are helpful. However, other factors, such as politics, societal customs, and
prescription practises, may be linked to the observed variances (Bending, Hutton, and
McGrath 2012).

Public guidance for health technology evaluation is available and based on manufacturer-
submitted evidence in the four nations studied by Vega et al. (2016), who compared HTA
processes and recommendations in Australia, England, the Netherlands, and Sweden. England
uses independent therapeutic assessment groups. England would pay for an explicit ICER
threshold. All four countries have high HTA listing recommendations, however settings vary.
Study demonstrates inadequate to moderate listing recommendations agreement. This
disparity may be due to the timing of HTA evaluations, status of drugs (Orphan vs non-
Orphan), categories of medicines with low value for money, HTA processes, how submitted
evidence is evaluated, national preferences, regulatory framework, and overall
recommendation-making process. The appraisal process's social values need further study
(Vega et al. 2016).

A study examined the clinical data evaluated by HTA agencies and their reimbursement
recommendations in England, Wales, Australia, and Canada. The results show that the HTA
bodies made the same recommendations four times and different recommendations five
times. Each HTA body bases its recommendations on efficacy and cost effectiveness. HTAs
assessed the same drug using many comparators and trials. PBAC (Pharmaceutical Benefits
Advisory Committee) and NICE included indirect and mixed comparisons, but Canadian CDR
/Common Drug Review) did not. CDR and/or NICE excluded the trials if the drug and/or
comparator were not used according to the applicable approved licence. PBAC, CDR, and NICE
use different clinical evidence for drug-listing recommendations. Treatment comparison data and medical practise in each nation affected evidence (Spinner et al. 2013).

According to a study evaluation criteria in all nations include efficacy, safety, relative efficacy, and economic data comparing several EU HTA bodies at varying stages of development in the use of HTA. The primary goals of the reasonably advanced HTA implementation group, which includes England, are to improve care quality, provide universal access, and make efficient use of available resources. However, even though these less developed nations have HTA bodies and norms in place, they frequently follow the advice of more developed nations when it comes to putting them into practise. These nations place greater emphasis on HTA as a means of cost estimation and on the financial effects of new medicines. HTA bodies have been established in both well-resourced and less-resourced nations. When deciding whether or not to establish an HTA body, governments may learn from the practises of others (Beletsi et al. 2018).

There are two different HTA methods used to determine the value of new medications in Europe. The quality-adjusted life-years (QALYs) gained by patients treated with a new pharmaceutical must be demonstrated in order for the government of some countries, such as the United Kingdom, to approve the medicine's price and provide citizens with access to it. Comparing clinical outcomes with those of currently available treatments is key to the evaluation of added value in other nations, including France. There are benefits and drawbacks to both the English and French approaches, and they have been weighed and compared. Similar results were discovered between English and French evaluations of the value brought about by new pharmaceuticals. On the contrary, the English method is more open and stimulates more political debate because of this. There appears to be convergence
between the two strategies, as both England and France announce price discussions in secret, and France announces a new necessity to estimate cost-effectiveness (Drummond et al. 2014).

2.3.6 Study framework for HTA recommendations

The differences in HTA recommendations contribute to the access to medicines gap, despite the fact that improving access to medications is a priority at the national level in many countries. As a result, it is crucial to understand the factors that contribute to variations in the recommendations-making procedure. A study presented and directed a methodical framework with the intent of investigating the contextual variation in HTA recommendations. For selected case studies, this framework is comprehensive and sheds light on recommendation-making practices (Nicod and Kanavos 2016).

2.3.7 Comparison of UK and European HTA recommendations

According to a study, patients in Wales have faster access to new drugs than those in England. When available, the All-Wales Medicines Strategy Group (AWMSG) adheres to the recommendations made by the National Institute of Health and Care Excellence (NICE). However, AWMSG evaluates drugs for which NICE guidance is not yet available, and its recommendations are replaced by NICE guidance if and when it becomes available. It was found that, in general, recommendations from different HTA groups in the UK were quite similar (Varnava et al. 2018).

NICE recommendations are more stringent than those of the Scottish Medicine Consortium (SMC). All new drugs are evaluated by SMC, but only a subset of new medicines are evaluated
by NICE. Although the Scottish Medicines Consortium relies on company submissions alone, NICE also incorporates independent experts’ opinions. There are benefits to relying on an outside party for assessment, but doing so may increase costs and lengthen the process, thus, a hybrid approach is recommended (Barbieri, Hawkins, and Sculpher 2009).

A study compared the recommendations of the Canadian national HTA with those of the HTA bodies in Australia, Canada, England, and Scotland to determine what factors account for the differences between the HTA recommendations. Recommendation-making processes of HTA bodies are found to have some commonalities, such as an emphasis on clinical efficacy and cost-effectiveness. Organizational approaches to risk perception and the choice of comparator in clinical and cost-effectiveness studies may account for the observed variation in recommendations. Uncertainties in areas such as cost-effectiveness, choice of comparator, clinical benefit, safety, trial design, and timing of submission are only a few of the reasons why novel medicines have been given a negative recommendation. This research shows that the HTA recommendation process can be influenced by a number of circumstances, leading to potentially contradictory results (Allen et al. 2017).

Analysis of HTA recommendations in five countries in another study suggests that HTA methodologies may be influenced by priorities, therapeutic area, levels of evidence, perceptions of value, uncertainty management strategies, and the ability and willingness to consider and implement risk sharing agreements (England, Scotland, Sweden, Canada, and Australia). As such, HTA organisations should provide clearer guidelines on whether or not a manufacturer is expected to demonstrate that the new medicine is more successful than
placebo or alternative treatments. More research needs to be done to fully understand and quantify the evidence given and how it may affect the assessment in various therapeutic applications (Nicod and Kanavos 2012).

According to a study, the German FJC (Federal Joint Committee) notably deviates in its recommendations from established HTA authorities in England, Scotland, and Australia. This study finds that the FJC appraisal is more stringent than NICE, which can be related to differences in agency missions, features, and the recommendation-making process, as well as the repercussions of a bad recommendation for patient access (Fischer, Heisser, and Stargardt 2016).

Comparing the HTA recommendations for orphan medicines for rare diseases in Scotland and the Netherlands, a study found that a much higher percentage of orphan drug applications were approved for reimbursement in the Netherlands (95%) than in Scotland (21%). Furthermore, the majority of submissions (24 of 37) in Scotland contained cost-effectiveness or cost-utility evaluations, while in the Netherlands, only 1 of 38 applications did so (Vegter et al. 2010).

Using records of HTA recommendations from both Canada and England, a study analysed the impact of clinical and cost-effectiveness evidence on HTA recommendations in both countries. The study found a wide range in the proportion of favourable recommendations, from 48% for NICE to 95% for Canada's national approach. Low levels of agreement were also discovered between agencies when making HTA recommendations. In several circumstances, progression-free survival data was considered sufficient rather than overall survival data in order to make a positive recommendation. Once the HTA process was complete, different
methods were adopted in each jurisdiction to address cost-effectiveness. A negative recommendation from NICE was likely in such instances, but a good recommendation with a mandatory pricing agreement was more likely from Canada’s process (Chabot and Rocchi 2014).

The HTA bodies in both the United Kingdom and Spain only evaluate carefully selected drugs. With more HTA bodies and less complicated procedures, Spain has been found in this study to have evaluated more drugs than NICE has for medicines that have been assessed by both organisations. NICE rejections outnumber Spanish committee rejections. Spanish organisations are more likely to prescribe cancer treatments for subpopulations of individuals where better outcomes can be gained, whereas NICE applies cost-effectiveness thresholds in their appraisals, resulting in a 'not recommended' recommendation in many cases. It takes Spanish Committees less time to make decisions than it does for NICE, probably because of the less complicated appraisal process in Spain (Blázquez et al. 2015).

2.3.8 Health Economic Evaluation

A study compares the data needs and availability for health economic (HE) evaluations in Poland, the Czech Republic, Slovakia, Hungary, and Romania and five other countries in Central/Eastern Europe (CEE) and five other countries in Western Europe (WE) (the United Kingdom, France, Germany, The Netherlands, and Sweden). The study shows that health economic evaluations (HE) are required for reimbursement applications in most countries. Most of the time, cost-effectiveness and budget-impact analyses are used in health economic evaluation. The preferred outcome of the cost-effectiveness analysis is quality-adjusted-life
years. At the time of the survey, the rules could not be found in Romania, France, or the Czech Republic. In Sweden and the United Kingdom, the HE evaluations dossiers are usually put together by the licence holder. Specifically, the United Kingdom, Poland, and Slovakia have a tendency to pay up to a specific threshold. Several nations, including the Netherlands, Sweden, France, and Poland, are advocating for a more holistic approach to CE analysis. Although the HE analysis needs are the same in both CEE and WE, researchers found discrepancies in the accessibility of health economics data. Information gathering is less of a hassle in Western Europe than in Eastern or Central Europe. Because of this, the results of HE evaluations in Central/Eastern Europe (CEE) countries are not as accurate as they could be (Skoupá, Annemans, and Hájek 2014).

The health economic evaluation has had minimal effect on limiting access to high-cost medications, according to a study that compared its use in four European countries, three of which have adopted it (England, the Netherlands, and Sweden) and one that has not (Germany). Despite the fact that economic evaluation has helped certain nations negotiate lower drug prices, it has also shifted the focus of the clinical efficacy debate to include consideration of the drugs’ price tags. Health economic evaluation may best be understood as a form of rhetoric due to the similarities between various approaches and the results they produce (Franken et al. 2016).

2.3.9 Use of Real-World Data in Health Technology Assessment

According to a study cost-effectiveness analyses (CEAs) were more likely to incorporate real-world data (RWD) than relative effectiveness analyses (REA. The five agencies’ approaches to including RWD in REA varied; some focused solely on prevalence and incidence data, while others also included RWD when discussing the efficacy and safety of drugs. Meanwhile, there
was no discernible development in the percentage of real-world data used over time. However, due to variations in methodology and annual report output, these findings should be viewed with caution. The optimal setting for the application of RWD in HTA practise is within Conditional Reimbursement Schemes (CRSs), which are implemented by several HTA agencies and cover a wide range of disease indications. Future studies should investigate this area (Makady et al. 2018).

A study also examined the policy of six European HTA agencies on the use of RWD in the REA of pharmaceuticals. Multiple HTAs have different policies on the use of RWDs. These variants may discourage RWD for use with HTA. It appears that more policy alignment is needed across Europe to make it easier for RWD to be used for HTA. This may be possible with the help of recent papers and project ideas from the European network of HTA. Future studies should examine whether actual RWD implementation varies from official policy (Makady et al. 2017).

2.3.10 Comparative Effectiveness Research (CER)

A study examined the role of Comparative Effectiveness Research (CER) in drug coverage recommendations and, to a lesser extent, pricing decisions across six European countries (Denmark, England, France, Germany, the Netherlands and Sweden), CER has become increasingly influential in these areas. This not only helps in the discovery of the most cost-effective medications, but it also assists in the development of evidence-based recommendations. Researchers found that there is no one right way for countries to apply CER to determine drug coverage (Sorenson 2010).
2.3.11 Relative Effectiveness Assessment (REA)

A study examined potential roadblocks and essential success criteria for establishing European collaboration in the area of relative effectiveness assessment (REA) of pharmaceuticals. Challenges to its implementation and adaptation at the national level, as well as methodological and financial considerations, were identified in the study. Collaboration with knowledgeable partners, high-quality evaluations, and fast results were crucial to the success of international assessments. More fine-tuning of the procedure and approaches is needed for optimum cooperation (Kleijnen et al. 2015).

A study compares the pricing or reimbursement recommendations for medicines in six EU countries based on their guidelines and relative effectiveness assessments (REAs) (England, France, Germany, The Netherlands, Poland, and Scotland). A look at the guidelines shows that clinically and patient-related end points (such as Overall Survival (OS) and Quality of Life (QoL)) are preferred over surrogate end points. It was found that all REAs include information about overall survival if it is available, but this information is not very strong. Most of the guidelines do not say much about progression-free survival (PFS), and different studies and HTA bodies have different ideas about how important it is. It was found that PFS data are in 70% of the REAs. QoL data was used in 54% of relative effectiveness assessments, but it did not have much of an effect on the HTA recommendations. In the EU, regulators are now willing to accept some uncertainty in clinical evidence. This has made it harder for HTA to make recommendations on the relative effectiveness of new medicines because there are gaps between the clinical evidence that is requested and the clinical evidence that is available. The results of the study show that a discussion with many different people would help solve this problem (Kleijnen et al. 2016).
2.3.12 Pricing

2.3.12.1 Impact of Regulatory approach VS Market Environment on Pricing

Prices in a country are established either by government regulation or by the way the market works. In the UK, the cost-effectiveness analysis is used by NICE to set prices for new medicines, which is a more formal way of regulating. But prices in the US are not set by the government. Instead, they are set by the free market. Even though value-based pricing in both countries is driven by different systems (regulation vs. the market), it cannot be proven that these different systems lead to different results (Comanor et al. 2018).

2.3.12.2 Health Technology Assessment & Reference Pricing

In order to get the most for their money, countries use reference pricing and HTA to make funding suggestions. Reference pricing cannot be used in every case, though. Health technology assessment is a much better way to do things, but the reference pricing could help in pricing and paying for drugs that offer almost the same treatment value as the medicines that are already on the market. At different times, different EU countries have taken more than one approach. A study looked at how these things are done in Germany, the Netherlands, Sweden, and the UK and found that a two-pronged approach is becoming more common. This makes HTA a key policy for figuring out whether something is worth the money, which is supported by reference pricing. Countries like the Netherlands and Germany are moving toward this two-pronged approach, while the United Kingdom has only used the HTA policy (Drummond et al. 2011).

2.3.13 Risk-Sharing Agreements, Managed Entry Schemes, and Patient Access Schemes

Some new, expensive medicines are being given the green light through risk-sharing agreements, even though there is not a lot of evidence (clinical or cost-effectiveness) to back
them up. Weak evidence makes it difficult to figure out how to pay for these medicines, so the final recommendations come with a risk. To deal with this, risk sharing agreements are being made to deal with the uncertainty that comes with these risks and to help patients get these medicines when they need them (Ranson 2018).

In order to put a number on the risk involved in HTA recommendations, a study presents an HTA risk analysis chart that looks at the payer strategy and uncertainty burden (P-SUB). By providing a standardised notion to demonstrate the need and possible usefulness of various MEAs, this helps people with recommendation authority identify those situations. If implemented, HTA has the potential to ensure that MEAs are routinely, consistently, and openly considered. It is expected to be useful both for payers and the industry in the dynamic new pharmaceuticals landscape (Grimm et al. 2017).

Currently, there is an increase in the number of MEAs, and this trend is expected to continue. A recent study, looked at how different EU countries use MEA for different drugs despite having the same active ingredients. A greater number of contracts are discovered to be monetary in nature as opposed to performance based. Outside of Italy, performance-based contracts are not widely used across the European Union. The usage of performance-based agreements has also been abandoned in the Netherlands, as it is incompatible with market forces. Sales promotions such as price cuts and free stock are common in England. Evidence development is also a priority in the Netherlands and Sweden. There is an amalgamation of English, Swedish, and Dutch methods used in Belgium. It appears that the motivations behind the implementation of various MEAs are the same across nations (Pauwels et al. 2017).
A study found that the use of MEAs varies significantly between countries and between indications for the same drugs. Differences in health care systems are likely to be responsible for these discrepancies in MEA deployment. The degree of uncertainty, the ability to pay, the relative cost-effectiveness, and the influence on the general budget are additional assumptions connected to these MEAs changes. Additional studies are needed to understand the factors that contribute to countries' varying rates of MEA implementation (Pauwels et al. 2017) (Ferrario and Kanavos 2015).

Respondents to a survey among payers in North America, Europe, and Australasia reported that secret discounts are the norm and are typically applied to speciality medications. The survey also found that the prices that customers actually paid to the manufacturers differed little from the listed rates (Morgan, Vogler, and Wagner 2017).

In order to better understand the potential policy implications of future innovative pricing agreement (also known as MEA) ideas, a study surveyed EU payers. Respondents to the survey were positive about the future of creative pricing arrangements and expected their use spread throughout the EU. However, it is not assumed that it will be a cookie-cutter solution, as these agreements need to be adapted to the unique requirements of individual therapeutic areas, healthcare systems, and payer expectations. More studies are needed to conduct a survey with a larger sample size and in other regions by delving deeper into payer preferences (Dunlop et al. 2018).

The National Health Service (NHS) in the United Kingdom has partnered with pharmaceutical companies through patient access schemes to gain access to expensive medications. NICE drives these schemes to resolve the uncertainty for high-cost drugs. Instead of lowering list
prices, UK financial schemes offer reductions and rebates. The study does not corroborate the motivations for these arrangements. Due to the confidential discounts and rebates agreed with payors in patient access schemes, reference pricing is difficult to grasp. Therefore, a clear and fair assessment of these schemes is needed (Jarosławski and Toumi 2011).

To help the National Health Service (NHS) in England pay for cancer drugs that are not covered by NICE, the Cancer Drug Fund was established in 2010. There is no evidence that the considerable expenditures allocated to this programme have given significant benefit to patients. As part of a larger overhaul in July 2016, this initiative is now known as the controlled access fund (Aggarwal et al. 2017).

For medical services that are fully or partially covered by insurance, patients are responsible for making a copayment. The abolition of co-payments in Wales had a small but positive effect on dispensing rates, as reported in a study. The amount of the decreases in copayments is comparable to that shown in other studies (Alam et al. 2018).

2.3.14 Involvement of stakeholders and views on the reimbursement process

The different members of funding bodies, especially those responsible for making recommendations, each have their own preferences and points of view that should be taken into account. Depending on the member’s position and responsibilities, there can be significant differences in opinion (Ratcliffe et al. 2009).

Rationing health care is necessary due to limited resources, yet spending precious monies effectively requires a methodical strategy. Stakeholders should actively seek the perspectives of individuals, such as the general public, who are not normally included in the recommendation process when reaching an agreement becomes difficult (Moreira 2011).
When deciding what should be prioritised, it is important to get public feedback. According to a recent study, the public does not place a high value on funding suggestions for orphan medications at a higher cost-effectiveness threshold. These results have implications for the suitability of present practises of recommending the orphan medications at a very high threshold, especially in light of the increasing prevalence of these diseases and the expensive price of their treatments (Bourke et al. 2018).

A study into the involvement of stakeholders by Health Technology Assessment Organisations in France, Spain, England and Wales, Germany, Sweden, and the Netherlands reveals that the NICE includes all relevant stakeholders in an HTA process and in the subsequent recommendation making process. In the United Kingdom, businesses have a voice in all evaluations. The recommendation-making process features extensive participation from all relevant parties, typical of the administrative approach taken in the United Kingdom. The findings of this research suggest that the success of a stakeholder engagement strategy in one nation is undermined by the fact that its implementation in another country is complicated by the fact that health care systems in those countries have different administrative styles and objectives (Cavazza and Jommi 2012).

Stakeholder participation in priority setting and appeals processes for six medicines was studied across five drug reimbursement recommendation committees in Australia, Canada, England, and the United States. America, Israel, and Wales. It was found that clinicians, researchers and members of the public were the most active participants. There was a discrepancy in the proportion of industry representatives on certain committees. Except in Israel and the United States, all the countries analysed allowed pharmaceutical companies to legally appeal the recommendations. Stakeholder categories, their levels of participation in
the overall evaluation, and the procedures for handling amendments and appeals differ. The 
research revealed a diverse set of already involved parties, as well as additional parties that 
the researchers felt were necessary. It was agreed that a fair and genuine procedure for the 
reimbursement of new pharmaceuticals would result from including all important 
stakeholders in the discussion (Yunger et al. 2012).

2.4 Discussion

2.4.1 Access to Medicines in the United Kingdom and Europe

This systematic review shows that medicines availability varies between EU member states, 
including the United Kingdom, as shown by the included studies. Despite encouraging 
progress toward the World Health Organization's objective of universal health care in the 
European Union, many people still lack access to life-saving medications (Cylus and 
Papanicolas 2015). The time it takes for new medications to enter different European markets 
is a major factor in the wide range of drug availability across the continent. Shorter times 
between licencing and reimbursement filing, having a local sales rep, having proof of 
therapeutic benefit before launching, and having a large market all contribute to a quicker 
time to entry for pharmaceuticals. Although significant attention is paid to early access, the 
study makes no observations on whether or not this results in lasting effects (Ferrario 2018).

Access to medicines is variable across different categories of medicines including those for 
rare diseases and is impacted by high costs, insufficient efficacy/safety evidence, and societal 
preference for funding orphan treatments (Detiček et al. 2018).

The number of medications, the newest medicines, and the most innovative medicines 
fundied by the UK government is higher compared to the corresponding figures for the US, 
Australia, and New Zealand. There is some variation in access to different types of drugs
across the UK, and the country is slow at reimbursing new medicines compared to other EU countries (ABPI n.d.). Japan appears to have relatively higher insurance coverage and more access to a wider number of medicines when compared with EU countries including the UK (Takayama and Narukawa 2017). Researchers have found that patients in Wales get new medicines faster than those in England (Varnava et al. 2018). Although more money must be spent, new medicines need to be prioritised so that patients in the UK can get them as soon as possible (ABPI n.d.).

2.4.2 UK and European HTA

This review looks at a number of studies that look at a number of aspects of health technology assessments. It is very important to look at HTA recommendations in terms of how they affect patient access. One of the studies in this review shows that negative and restrictive HTA recommendations have a financial effect on the NHS. However, another study shows that negative and restrictive HTA recommendations do not really change the rate and cost of prescriptions. This could be because prescribers don’t follow HTA recommendations, or it could be because the HTA bodies that make recommendations and the local health service do not have the same goals (Dietrich 2009).

NICE, the National Institute for Health and Clinical Excellence, evaluates the effectiveness of medical technologies. In most cases, NICE only evaluates drugs that have been referred to it by ministers (unlike the SMC, which appraises all new medicines when they receive a licence). The National Health Service (NHS) in England and Wales is required by law to follow the recommendations set out by NICE. The Northern Ireland Department of Health (DH), Social Services (DSS), and Public Safety (PSNI) is connected to NICE and evaluates all NICE recommendations to determine if they are relevant to NI (Payne 2012). Additionally, the
Department of Health (DH) in Northern Ireland considers the suggestions of SMC. Even in the absence of NICE or SMC guidelines, the Department of Health of Northern Ireland will conduct a case-by-case examination of products (Ranson and Llp 2019). The Northern Ireland Department of Health declared in September 2018 that it would take steps to expand citizens’ access to cutting-edge cancer and other disease treatments. The goal of the new approach is to give people living in Northern Ireland the same access to cancer medications as people in the rest of the United Kingdom(Department of Health 2018a). When available, the All Wales Medicines Strategy Group (AWMSG) adheres to recommendations made by the National Institute of Health and Care Excellence (NICE). However, AWMSG evaluates drugs for which NICE guidance is not yet available; in such cases, its recommendations would be superseded if NICE guidance became available at a later date (Varnava et al. 2018). There was no discernible external factor that affected the All Wales Medicines Strategy Group (AWMSG) HTA recommendations contained in this review (Neill and Devlin 2010).

Newly licenced medications, new formulations of existing medicines, and new indications for current drugs are all topics on which the Scottish Medicines Consortium (SMC) advises NHS Boards and their Area Drug and Therapeutics Committees (ADTCs) across Scotland (licensed from January 2002). All newly authorised medicines will have a recommendation from the SMC issued to NHS Scotland as soon as possible after the product launch, at the latest (Developed and Consortium n.d.). Recommendations for SMC reimbursement in Scotland are heavily influenced by the findings of cost-effectiveness evaluations(Aggarwal and Sullivan 2014). Scotland's SMC is more lenient in its criticism of drugs than Poland's, and Scotland's HTA criteria are more detailed than those of Poland's, giving producers more information with
which to fill out their HTA applications (Kolasa and Wasiak 2012). Compared to France, Scotland recommends less medicine than France does (Bending et al. 2012).

In countries that have been using HTA for a while, its main goals are to improve the quality of care, ensure that everyone has equal access, and make the best use of resources. Countries that are not as far along in their development often follow the advice of countries that are further along. These countries pay more attention to how new medicines affect their budgets and how HTA can be used to estimate costs (Beletsi et al. 2018). In England, there is public advice on how to evaluate health technologies, and the evaluations are based on the evidence that the manufacturer sends in (Vega et al. 2016).

Reviewing HTA practises, processes, and policies in the EU and the UK shows that there are differences. These differences come from the different priorities of people who make recommendations, as well as the different ways each country implements recommendations and sets up a framework for doing so (Angelis et al. 2018). When the HTA recommendations of different EU countries are compared, they show that there is moderate to poor agreement. Reasons for this disparity include variations in national preferences, regulatory frameworks, the timing of HTA assessments, the status of medicines (Orphan vs. non-Orphan), the types of medicines that offer low value for money, HTA processes, how the submitted evidence affects the evaluation, and HTA processes (Vega et al. 2016). The recommendations of each HTA body are based on a different set of evidence. There were differences in the evidence due to how each country looked at indirect and mixed treatment comparison data and how medicine was done in each country (Spinner et al. 2013). In all countries, HTA evaluation criteria are usually based on how well it works, how safe it is, how well it works compared to other treatments and how much it costs (Beletsi et al. 2018).
Gains in health, measured by quality-adjusted life years (QALY), are used to justify the cost and availability of a new pharmaceutical in several EU (European Union) countries like the United Kingdom. Clinical outcomes relative to already available treatments are evaluated in other countries, such as France, to determine added value. Similar results were discovered between English and French evaluations of the value brought about by new pharmaceuticals. On the contrary, the English method is more open and stimulates more political debate because of this. They appear to be moving in the same direction, with England’s private price discussions and France’s recently announced necessity to determine cost-effectiveness converging (Drummond et al. 2014).

Overall assessment outcomes (i.e., positive, negative, or restricting recommendations) in the United Kingdom are not totally aligned but shown to be nearly equivalent between different HTA organisations. It appears that Welsh patients have better access to drugs than their English counterparts (Varnava et al. 2018). NICE recommendations are more stringent than those of the Scottish Medicine Consortium (SMC), allowing them to encompass special populations. Although the Scottish Medicines Consortium relies on company submissions alone, NICE also incorporates independent experts’ opinions (Barbieri et al. 2009).

The research found certain commonalities in the way these HTA organisations reached their recommendations. HTA organisations typically prioritise clinical effectiveness and cost-efficiency. All have a minimum QALY that they must maintain (Allen et al. 2017). Risk perception and unknowns in many areas, such as cost-effectiveness, comparator choice, clinical benefit, safety, trial design, and submission time, may account for variations in HTA recommendations (Allen et al. 2017). It is also due to the fact that HTA bodies have varying goals and preferences, as well as therapeutic area, evidence levels, value perceptions,
uncertainty mitigation methods, and the willingness and ability to implement risk sharing agreements (Nicod and Kanavos 2012). This also involves variations in the functions, characteristics, and procedures of the agencies involved in the recommendation-making process, as well as the repercussions of a recommendation that is unfavourable for patient access (Fischer et al. 2016).

In terms of comparative efficacy, the German FJC (Federal Joint Committee) is expected to apply stricter criterion requirements than the NICE (Fischer et al. 2016). It was found that a much higher percentage of orphan medication reimbursement requests were granted in the Netherlands (95%) than in Scotland (21%). In addition, unlike in the Netherlands, most Scottish proposals also included cost-effectiveness or cost-utility evaluations (Vegter et al. 2010).

Unlike the United Kingdom, Spain only approves carefully selected medications for evaluation in their country. There are more HTA bodies in Spain, and the procedures in Spain are easier, therefore, more drugs are evaluated there than by NICE. The rejection rate is higher than that of the Spanish HTA. Spanish organisations are more likely to endorse cancer treatments where improved outcomes are possible, in contrast to the National Institute for Health and Care Excellence (NICE), which uses cost-effectiveness thresholds in its appraisals and so issues numerous "not recommended" recommendations. As a result of Spain's more straightforward evaluation methodology, Spanish Committees are able to complete their work more quickly than the NICE (Lozano-Blázquez et al. 2015).

Although health economic evaluation is required for reimbursement requests in most European Union member states, including the United Kingdom, Germany has not generally
adopted this practise (Skoupá et al. 2014)(Franken et al. 2016). Common methods of health economic evaluation include cost-effectiveness analysis and budget-impact evaluations. Cost-effectiveness analysis favours QALY as a metric of success. Health economic evaluation has been called "rhetoric" by its detractors because it has been shown to have no real effect in limiting patient access to costly medications (Franken et al. 2016).

Many different policies exist among EU HTA authorities regarding the usage of RWD. This systematic research finds that RWD is more commonly included in CEAs than REAs in HTA assessments. Depending on the situation, RWD can be used to determine therapeutic efficacy and safety or to determine the prevalence and/or incidence of a disease. It appears that more policy alignment is needed across Europe to make it easier for RWD to be used for HTA (Makady et al. 2018) (Makady et al. 2017).

This analysis verifies the growing importance of CER in European drug coverage recommendations and, to a lesser extent, pricing recommendations. While aiding in the development of evidence-based recommendations, it is also useful in identifying drugs that provide the greatest bang for the buck(Sorenson 2010). There is a preference for clinically relevant patient outcomes linked end goals (Overall Survival (OS) and Quality of Life (QoL)) over surrogate end points, as shown by an analysis of Relative Effectiveness Assessments (REAs) of pharmaceuticals for pricing or reimbursement recommendations. It was discovered that every REA has OS data, but that it is not always reliable. Seventy percent of the REAs were found to provide data on PFS. Although incorporated into 54% of REAs, quality of life data had a negligible impact on HTA recommendations (Kleijnen et al., 2016).
2.4.3 Pricing

Any country's prices are normally set by either a regulatory process or the free market. A country with a more formal regulated approach to determining prices is the United Kingdom, where the National Institute for Health and Care Excellence (NICE) uses cost-effectiveness analyses for cutting-edge pharmaceuticals. Instead of using a methodical methodology, the United States relies on market forces to determine whether or not an investment is worthwhile. It is not known whether or whether the different mechanisms (regulatory versus market) that promote value-based pricing in the two countries provide different results (Comanor et al., 2018).

After nearly 60 years, the Pharmaceutical Price Regulation Scheme in the United Kingdom was replaced in 2018 by a new 5-year agreement between the government and the pharmaceutical sector on the pricing of medicines (PPRS). An agreement in principle was reached with the Association of the British Pharmaceutical Industry (ABPI) on the new Voluntary Scheme for Branded Medicines Pricing and Access, which went into effect on January 1, 2019. The new plan limits the annual increase in sales of branded medications to the NHS to 2%, and pharmaceutical companies offer refunds based on net sales for any money spent beyond the budgeted amount. The NHS will realise an estimated saving of £980 million as a result of this. For their part, businesses hope to receive "more and faster NICE reviews for new drugs," maybe six months earlier than is the case now. In theory, this will alleviate pharmaceutical firms' concerns that the United Kingdom has a slower rate of adopting new drugs than other European countries (December 2019)(Taylor 2018).
2.4.4 Risk-Sharing Agreements in UK and Europe

When the clinical evidence and financial implications of a new treatment are unclear, the pharmaceutical industry and organisations with financing approval authority may enter into an arrangement known as a managed entry agreement (MEA). Due to this ambiguity, pharmaceutical companies and insurance companies have developed MEAs to divide the risk (Pauwels et al. 2017). The prevalence of MEA is rising, and their use is only projected to increase further in the coming years (Pauwels et al. 2017). Due to differences in therapy areas, healthcare system architectures, and payers' expectations, it is unrealistic to assume that there will be a universally applicable model for these agreements (Dunlop et al. 2018). When comparing the two main types of contract, the financial agreement is far more common than the performance agreement. There is a lack of widespread use of performance-based agreements in the rest of the EU, with the exception of Italy. In the Netherlands, performance-based contracts were once employed but were eventually abandoned because they were ineffective in a market economy. Patient access programmes, which provide vouchers for reduced prices or even free medication, are widely used in the UK. Due to the nature of the rebates negotiated with PAS scheme payors, a clear and fair method is necessary to aid in the assessment of these schemes. To better understand the effectiveness of these programmes, the Netherlands and Sweden have placed a significant emphasis on evidence development. All of the aforementioned methods are used in Belgium. Although the motivations for introducing MEAs appear to be the same across nations, it is unusual for the same drugs to have MEAs implemented in multiple EU member states. The same drug is often available in several different forms in countries that use MEAs. Differences in health care system administration are likely contributing factors to the different rates at which these countries
have implemented MEAs. Uncertainty, financial resources, and relative cost-effectiveness and fiscal impact are some other underlying assumptions connected to these many MEAs (Pauwels et al. 2017) (Ferrario and Kanavos 2015).

In 2010, the Cancer Drug Fund was established in England to help the NHS pay for cancer drugs that had not been given the green light by the NICE. Despite a large budget, there is no evidence that patients have benefited from this initiative. In July 2016, after implementing a number of adjustments, NICE released a revamped programme and rebranded it as a controlled access fund. This allows drug access for up to two years before another submission to NICE is necessary. NICE will decide whether to reinstate the drug’s recommendation for use or withdraw it at the time of resubmission for standard funding (Aggarwal et al. 2017) (Cancer Research UK 2018).

2.4.5 Co-Payments

Many countries, including the United Kingdom, require copayments for prescription drugs in the form of a flat fee per item issued to patients as a means of offsetting the rising expense of healthcare. Until the Welsh Government froze the co-payment in 2000 and totally removed it in April 2007, the co-payment was treated the same way throughout the rest of the United Kingdom. The inability of low-income people to pay for their medications due to these co-payments is a serious concern. It was reported that the elimination of co-payments in Wales increased dispensing rates, however this effect was not proven to be statistically significant (Alam et al. 2018).
2.4.6 Stakeholders' Reimbursement Views

Stakeholders' perspectives differ from one another because they are tied to the specific responsibilities that each plays inside an organisation. (Ratcliffe et al. 2009) These divergent opinions are a product of the different management philosophies and budgetary agendas of the several healthcare systems in existence (Cavazza and Jommi 2012). As opposed to bureaucratic recommendations, socially resilient ones are easier to implement since they involve a higher volume of buy-in from relevant parties. Therefore, when consensus cannot be reached, organisations must actively solicit the opinions of members, such as the general public, who are typically excluded from the recommendation process (Moreira 2011).

2.5 Limitations

Only studies published in English met the inclusion criteria. Nothing has been included if it has been published in a language other than English. Publication bias has not been evaluated for the studies included in this overview. There may have been bias in the decision to publish or not publish the studies, depending on the nature and motivations of the funding, neither of which can be reliably determined. We cannot rule out the possibility of publishing and outcome reporting bias, which may have resulted in the publication or non-publication of articles based on the type or direction of the finding.

2.6 Future Research

There are opportunities for countries to learn from each other and collaborate as the regulatory and reimbursement environment for pharmaceuticals changes and develop at various rates. Additional comparative studies are required to investigate the availability of medicines in each United Kingdom country are required.
2.7 Conclusion

Based on this analysis, it appears that access to different types of drugs and different countries within the United Kingdom and the European Union (EU) can vary significantly. Differences in the reimbursement and pricing process, agency mandates, characteristics, and the recommendation-making process, stakeholder/societal preferences, evidence requirements to support reimbursement, interpretation of submitted evidence, and non-adherence to reimbursement recommendations all play a role in the aforementioned variability in access to medicines. The National Health Service (NHS) of the United Kingdom bases its recommendations for payment of medications on feedback it receives from various health technology evaluation agencies. The results of appraisals conducted by several HTA groups in the United Kingdom are found to be almost the same, despite the fact that they are not totally synchronised. There is a pressing need for additional comparative research to investigate the current state of access to medicines throughout the United Kingdom.
Chapter 3: Methods

3.1 Introduction

This chapter will first discuss how to choose a research philosophy, followed by the research design, along with the benefits and drawbacks of the various research methods. This will be accompanied by a discussion of their ability to generate valid results that meet the thesis goals and objectives. Sample size and sampling strategy, as well as the data analysis techniques used, are discussed later in the chapter. This chapter illustrates the methods adopted by this research project to achieve its aims and objectives. The first objective of this research was to conduct a systematic review of the literature on access to medicines in the UK context. The purpose of a systematic review of the literature was to critically review and analyse the original research articles on the broader issue of access to medicines in the UK. The remaining objectives of the research in this thesis come from the systematic review of the literature performed and published by the researcher (Abbas et al. 2019) and presented in Chapter 02 of the thesis. This review showed that access to medicines is different in all countries and for different kinds of medicines. Access to medicines varies due to many things, including differences in health technology assessment, reimbursement, and pricing processes, agency mandates, characteristics, and recommendation-making processes, stakeholder and society preferences, differences in the evidence needed to support reimbursement, how submitted evidence is interpreted, and not following reimbursement recommendations. Health technology assessment (HTA) has become a key part of making pricing and reimbursement recommendations. Because of this, it is seen as a more important factor in access than factors farther away. It is very important to look at HTA
recommendations in terms of how they affect patient access. This review has shown that more research needs to be done on how people in different parts of the United Kingdom get access to medicines (Abbas et al 2019).

There are multiple frameworks (Penchansky and J Thomas 1981; Policy 2000) to study various dimensions of access to medicines in countries with developed health care systems, which may not have significant supply chain problems but face more challenges in determining whether a new drug is good value for money, ensuring reasonable prices, and inclusion in the list of reimbursed medicines. Cohen et al., (2007) for example, defined eight sub-dimensions of patient access to medicines to conduct an international comparison of access. These include market authorization, the time of market authorization (MA), reimbursement, cost sharing, reimbursement terms, the time from MA to reimbursement, the degree to which beneficiaries may choose between various medicine benefit packages, and variability in coverage and cost sharing throughout the population (Cohen et al. 2007).

According to other researchers, the following factors, which include some of the factors mentioned above, have been recognised as determinants of medicine access in studies: out-of-pocket costs, country wealth metrics, drug financing, including increased funding for cancer medicines, budgetary constraints, HTA and coverage decisions, prescribing habits, MA time, availability of required expertise, specialisation, and equipment for administration (Benjamin et al. 2014; Cbe 2010; Cherny et al. 2016; Kelly et al. 2015).

Access is presented as a broad concept that summarises a set of aspects including availability, accessibility, acceptability, affordability, pricing, and reimbursement (Penchansky and Thomas 1981). The European Federation of Pharmaceutical Industries and
Associations (EFPIA) Waiting to Access Innovative Therapies (W.A.I.T.) indicator defines access as the rate of availability, which is measured by the number of medicines available to patients and usually marked by the time medicines get on the reimbursement list. It is also the average time between marketing authorization (MA) and patient access. This is measured by the number of days between the date of MA and the date that all post-MA administrative processes are completed (EFPIA 2019). A patient access indicator was made to show that countries that do well in time to market access do not necessarily do well on patient access. The patient access indicator focusses on the post-reimbursement phase of medicines, which is defined as "the phase that begins when the first patient is treated under a formal reimbursement scheme." Although most of the current literature and data focus on market access rather than patient access, keep in mind that just because something is on the market does not mean it is available to patients (Jansen and Amesz 2020).

3.2 Research Philosophy

In this section, the philosophical stance and preconceived notions of the researchers are described.

A research philosophy is a framework that guides how research should be conducted based on ideas about reality and the nature of knowledge (Collis 2013). A research paradigm is "the set of common beliefs and agreements shared between scientists about how problems should be understood and addressed" (Kuhn 1964) "A paradigm is a basic set of beliefs that guide action" (Guba 1990).

According to Guba (1990), research paradigms can be characterised through their:

- ontology – What is reality?
- epistemology – How do you know something?
- methodology – How do you go about finding it out?

Figure below shows how the research philosophy guides the development of a methodological approach.

Creswel (2014) is comprehensive in his treatment of the topic and acknowledges that the philosophical foundation of research is often hidden and that researchers should be more explicit in stating their position. He uses the term "worldviews" to describe what others have called paradigms (Mertens, 2010; YS Lincoln, 2011) and epistemologies and ontologies (Crotty 1998). Creswell identifies four worldviews summarized as follows.
Postpositivism: According to Creswell (2014), post-positivist research is based on the assumption that careful observation and measurement of an objective reality "out there" are possible. According to Watjana (2015), this paradigm accepts that "reality isn't perfect," but it also takes into account the biases that come from social interactions, or the way research is done. For post-positivists, research is sometimes based on values, but important biases are kept in check. When something is "value-laden," it means that the people doing the research are a part of it and may change the study. So, the postpositivist paradigm is the best way to describe the predetermined realms, and it suggests that the study use a survey or other quantitative methods (Watjana, 2016).

Constructivism/Social Constructivism: Creswell (2014) notes that this view is often combined with interpretivism and is built on the assumption that individuals have their own subjective views of reality, based on their own construction of meaning as they engage with the world within a historical and social perspective. According to Jonassen (1991), constructivism asserts that reality resides primarily in the mind of the knower and that the knower constructs or at least interprets reality based on his or her perceptions. Objectivism focusses on the object of our knowledge, whereas constructivism is concerned with how knowledge is constructed. The way in which one constructs knowledge is determined by one’s prior experiences, mental structures, and beliefs used to interpret objects and events. Constructivism does not deny the existence of an external reality; rather, it asserts that we each construct our own reality by interpreting our perceptual experiences of the external world. Constructivism does not say that there is no external reality. Instead, it says that each of us builds our own reality by interpreting what we see and hear in the outside world (Jonassen 1991).
Transformative: According to Creswell (2014), "This philosophical worldview focusses on the needs of groups and individuals in our society that may be marginalised or disenfranchised." The goal of transformative research is to lead to political or social change for the benefit of marginalised groups.

Pragmatic: The pragmatic worldview is often associated with mixed research because it "is not committed to any one system of philosophy or reality" (Creswell, 2014). Its concern is with the research problem itself and then employing whatever is needed to understand the problem.

Discussion and rationale for Choice of Research Paradigm

It has often been observed very accurately (Benbasat et al., 1987) that no single research methodology is intrinsically better than any other methodology, with many authors calling for a combination of research methods in order to improve the quality of research (Kaplan & Duchon, 1988). Equally, some institutions have tended to adopt a certain "house style" methodology (Galliers and Land 1987); this seems to be almost in defiance of the fact that, given the richness and complexity of the real world, a methodology best suited to the problem under consideration as well as the objectives of the researcher should be chosen (Benbasat 1984). In this research, we have tried to avoid what may be characterised as methodological monism, i.e., the insistence on using a single research method. This is not due to an inability to decide between the various merits and demerits of the various alternatives. Instead, we believe that all methods are valuable if used appropriately and that research can include elements of both positivist and interpretivist approaches if managed carefully.
The researcher is motivated by the notion that a qualitative or quantitative method alone would not adequately address the current topic (Johnson and Onwuegbuzie 2016) (Tashakkori and Creswell 2007). The author of this PhD thesis holds that pragmatism is compatible with the mixed-methods research strategy (Denscombe 2008). The PhD thesis is explanatory in character, and the research findings were motivated by concepts from the literature review and systematic literature reviews (SLRs) conducted (Chapter 2).

According to Creswell (2014), pragmatic paradigms do not adhere to a particular philosophy or reality system. The researcher is free to select any appropriate methodologies and procedures to address the stated research questions. In a mixed-methods study, the researcher can collect and analyse data using a variety of techniques. There are always historical, social, and political circumstances in which research occurs.

In accordance with the pragmatist approach, quantitative (the positivist paradigm) and qualitative (the constructivist paradigm) research methodologies were used to answer the research issues provided in this dissertation. In the section of this chapter that follows, the rationale for a mixed-method research design and the explanation for selecting an explanatory mixed-methods research design are presented.

3.3 Research Design

To achieve the aims and objectives of this research after the completion of a systematic review of the literature, two studies were conducted using a mixed methods research design.

Mixed methods Research design is a method of gathering, analysing, and combining quantitative and qualitative data to gain a greater understanding of a research issue than
either methodology might do on its own (Creswell and Clark 2017). A mixed methods
approach could be used to provide comprehensive information by answering a variety of
issues, to provide trust in results, to serve as a realistic replacement for an ideal single
method design, or to assist marginalised groups in their emancipation. (Bryman 1992;
Greene et al. 1989; Lawrenz and Huffman 2016).

According to researchers (Pole 2007) (Tashakkori and Teddlie 2010), mixed-method designs
outperform single method designs in three ways. They can address research questions that
other methodologies can not, provide stronger inferences, provide comprehensiveness, and
provide a greater range of divergent viewpoints. These justifications are similar to the
previous ones, but they emphasise the importance of the research question in determining
the validity of mixed methods research. A narrow question may necessitate a mono-method
approach, while a broad question or range of questions may necessitate a mixed-method
approach (Tashakkori and Teddlie 2010). Since access to medicines is a broad topic and
requires a range of questions, a mixed-method approach was considered suitable for this
research.

The timing, interaction, and superiority of each portion of the analysis can be used to
classify mixed-methods studies. These involve designs in which qualitative and quantitative
elements are carried out concurrently, independently, or as a subset of one another
(Creswell and Clark, 2017). The four main types of mixed methods design are triangulation
design, embedded design, explanatory design, and exploratory design. Figures below clarify
the purpose of mixing the methods and also guide researchers in selecting an appropriate
mixed-methods design based on the intent of their research (Warfa 2016).
The explanatory design is a mixed-method design with two phases. Collecting and analysis of quantitative data is the first step in this design. The subsequent compilation and review of qualitative data follows this first step. The second qualitative phase is structured to suit the findings of the first quantitative phase. Since this design starts with a quantitative approach, researchers usually put a greater focus on quantitative methods than qualitative methods. In an explanatory sequential design that uses mixed methods, the quantitative part or strand comes first. This is when all the quantitative data are collected and analysed. The qualitative data is collected and analysed. Finally, the complete interpretation comes from the qualitative data. So, the most important thing to remember about an explanatory sequential design is that the quantitative part of data collection and analysis comes before the qualitative part. This means that your quantitative results can affect or be a basis for your qualitative data collection and analysis. The main goal of using an explanatory
sequential design is to help explain your quantitative results. So, the explanatory sequential design is a mixed-method design, so it does have elements of pragmatism. However, because the quantitative and qualitative parts of the research are done separately, you have to think in terms of post-positiveism as you start your research using this design, and then you have to switch to constructivism. So you are really starting with post-positivism and then moving to constructivism (Creswell and Clark 2007)(Group 2015).

The explanation design has two variations: the follow-up explanations model and the participant selection model. While both models have a quantitative phase followed by a qualitative phase, the relationship between the two phases differs, with one concentrating on the findings to be tested further and the other on the relevant participants to be chosen. They also vary in terms of the relative importance given to the two phases (Creswell and Clark 2007).

**Explanatory Design: Follow-up Explanations Model**

![Follow-up Explanations Model Diagram](source)

This research work is an example of an explanatory design follow-up explanation model, as shown in the above figure. The follow-up explanations model is used when a researcher needs qualitative data to explain or expand on quantitative results (Cresswell et al. 2003). In study 01, quantitative data was collected and analyzed, and it was followed by the
collection and analysis of qualitative data in study 2. The quantitative part takes priority here and is followed by the qualitative part. The quantitative process helps to address descriptive questions and offers a general understanding of the research issue. Qualitative data and their interpretation aid in refinement and in-depth investigation. The approach in this mixed-methods research is predominantly inductive.

An overview of the thesis research, including both studies and a systematic review of the literature, is shown in Figure below.
Overview of Research

Aim
To Evaluate Access to Medicines Situation in the UK

Objective 1
To conduct SR of literature to critically review and analyse the original research on access to medicines in UK.

Objective 2
To study gap between licensing and health technology assessment

Objective 3
To study timelines from licensing to reimbursement of medicines

Objective 4
To study differences/variability in health technology assessment recommendation across countries in UK.

Objective 5
To study medicine uptake post-licensing and/or health technology assessment recommendation

Objective 6
To identify key challenges or barriers for access to medicines situation in UK.

Research Activities

CHAPTER 02
Systematic Review of Literature on access to medicines in the UK context

CHAPTER 04
Study 1: Document Analysis of Licensing and HTA Recommendations for new innovative medicines across the UK

CHAPTER 05
Study 2: A qualitative study exploring access to medicines situation in UK

CHAPTER 06
General Discussions, Study limitation, future work, Overall

Associated Objectives

Objective 1

Objectives 2,3,4

Objectives 2,3,4,5 & 6
The purpose of combining methods is distinct from the functions of individual methods in a study. A researcher can be explicit about each method's position in a study without actually being clear about how they relate to one another. Greene et al (1989) identify five purposes: triangulation, complementarity, expansion, development, and initiation, while acknowledging that multiple purposes can be active at the same time in a single study. Researchers mostly refer to the complementary use of methods in addition to triangulation (Barbour 1999) (Poole et al. 2000) (Sandelowski 2000).

Although the aim of this research project is explanatory, the research approach used in Study 01 is inductive, and that in Study 02 is deductive. These two approaches are not mutually exclusive, and combining induction and deduction is becoming more popular (Saunders et al. 2019), as the combined approach can provide a better understanding of a particular research subject.

3.4 Research Methods

This section describes the research methods used in this thesis, as well as a short explanation of each method, sample selection, and data collection and analysis procedures.

The principal methods used in this thesis include a systematic review of the literature (Chapter 02), document analysis of publicly available records and literature (Study 01-Chapter 04), and semi-structured interviews with the relevant experts to project the access to medicines situation in the UK (Study 02-Chapter 05). The researcher collected two types of data, i.e., primary data and secondary data.

The primary data was collected through semi-structured interviews with relevant experts in the pharmaceutical industry, and the secondary data was collected through document
analysis of publicly available records and literature. Having an explanatory sequential
design, this research adopted a two-stage methodological approach. First, a document
analysis of publicly available records and literature was performed, followed by semi-
structured qualitative interviews with relevant experts in the pharmaceutical industry. In the
table below, the pros and cons of the research methods (documentary research, document
analysis, and expert interview) are listed.
Table 2: Pros and Cons of Documentary Analysis and expert interviews

<table>
<thead>
<tr>
<th>Research Method</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documentary Analysis</td>
<td>• Information is easy to get</td>
<td>• Data may not be available; there may be mistakes in the original material;</td>
</tr>
<tr>
<td></td>
<td>• The data is cheap and easy to get, and the researcher doesn't have to be there when it's collected.</td>
<td>• There may be bias (called &quot;selective deposit or publication&quot;); data may be taken out of context;</td>
</tr>
<tr>
<td></td>
<td>• The data collection process makes sure that the records are unbiased.</td>
<td>• Preparation must be done in time before analysis.</td>
</tr>
<tr>
<td>Expert Interviews</td>
<td>• Ability to get specialised information from a subject and/or process expert</td>
<td>• Acquired knowledge is not neutral</td>
</tr>
<tr>
<td></td>
<td>• Give information and details that can't be found in other research methods or data sources</td>
<td>• Potential interaction effects (e.g., procedures not strictly standardised).</td>
</tr>
<tr>
<td></td>
<td>• Some kind of difference between interviewees makes it easier to get both high-level policy information and more detailed procedure information.</td>
<td>• Risk of anecdotal and illustrative 'knowledge'; not intersubjectively reproducible)</td>
</tr>
</tbody>
</table>

Sources: (Bogner et al. 2009) (Flick 2014)(Dunn et al. 2012)
3.4.1 Document Analysis in Study 01

The purpose of the document analysis was to review the licensure and health technology assessment recommendations for innovative medicines in the UK. Document analysis is the method of using documents as the object of study. Depending on the research objective, a document analysis can be either quantitative or qualitative. Document analysis as a research method often avoids ethical issues because the documents being analysed are in the public domain (Babar 2020).

Document analysis is one of the most widely used techniques in health policy research, and conducting policy research without it is virtually impossible (Dalglish et al. 2020). Documentary analysis, as in this project, is useful when a document exists that is relevant to your research question; when you realise that not analysing this (or these) document(s) will leave a gap in your research; and when observing or interviewing many subjects in your population is not possible. This method is an important part of health policy studies because it is quick and inexpensive. Using an organised system of analysis improves the procedural rigour of document analysis, allows for a more thorough understanding of policy process and content, and improves the efficiency of other approaches like interviews and non-participant observation (Traulsen and Klinke 2005).

3.4.1.1 Sample

The sample included 56 new innovative medicines licenced by the European Medicines Agency (EMA) in 2017 and their subsequent assessments by health technology assessment (HTA) bodies in the United Kingdom (UK) from the date of licencing of the medicines in 2017 until January 2020.
The information on new innovative medicines licenced by EMA, together with all related details, i.e., date of approval, licenced indication, category of medicines (orphan and non-orphan, oncology and non-oncology), licencing approval pathway, was extracted from the EMA website (European Medicines Agency n.d.) and is enclosed as Appendix 4. Definitions of "innovative medicines" and "orphan medicines" are provided in the Glossary and Definitions section.

3.4.1.2 Data Collection

Document Analysis gathered data on licencing and HTA recommendations, as well as the date of HTA recommendation for new innovative medicines. Information was collected from the portals of the relevant HTA bodies in countries across the UK. The study retrieved the HTA recommendations in all UK countries from the date of licencing the medicines in 2017 until January 2020.

To allow the review of HTA recommendations across jurisdictions, the HTA recommendations were classified as "recommend without restrictions," "recommend with restrictions," "not recommended," or "not assessed." The researcher had adopted Raftery’s approach, in which HTA recommendations were classified based on specific criteria (Kolasa et al. 2011). Recommendations without restrictions mean that treatment will be available to all patients covered under the approved licence. Recommendation with restrictions means that the treatment will be available to a subgroup of patients covered by the approved license. Not recommended means that the treatment will not be available to any of the patients covered under the approved licence. Not assessed means that an HTA assessment was not performed (Kolasa et al. 2011).
These sources of information are listed in the table below.

Table 3: Sources of information for Document Analysis

<table>
<thead>
<tr>
<th>Organizations</th>
<th>Documents to review available at internet websites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Department of Health, Social Services and Public Safety (HPSS) in Northern Ireland.</td>
<td><a href="https://niformulary.hscni.net/">https://niformulary.hscni.net/</a>&lt;br&gt;Formulary, Managed Entry Agreements</td>
</tr>
</tbody>
</table>

3.4.1.3 Data Validation

The researcher had retrieved data from the public domain and kept track of it. The supervisor then audited the completed database for accuracy against public domain sources, or the primary researcher performed the audit after a fair amount of time had passed since the initial database was completed.
3.4.1.4 Data Analysis

Descriptive statistics were used to present the percentage of HTA decisions classified as "recommend without restrictions", "recommend with restrictions," "not recommended," or "not assessed." The study results were further assessed for HTA recommendations linked to or without "managed access agreements." Decisions were also assessed to find differences between medicines categorised as orphan vs. non-orphan, oncology vs. non-oncology, and licencing approval pathways, that is, standard vs. non-standard. Fisher's exact test was employed for the data given in Tables 5–8 to find an association between HTA aspects and counts in different regions. A p-value of 0.05 was considered significant.

3.4.2 Qualitative Interviews in Study 02

Primary investigations, e.g., surveys, questionnaires, interviews, etc., are found relevant if the information from secondary data sources is not adequate. There are generally two approaches for administering a questionnaire: a self-administered questionnaire to be completed by the study participants or the questionnaire being administered by an interviewer (e.g., a semi-structured interview). In this research project, a semi-structured interview was used. Questionnaires and interviews are frequently used in mixed methods research (Brookhart and Durkin 2003). Although questionnaires can reveal trends in large populations, qualitative interview data can provide more in-depth information about participant perceptions, thoughts, and behaviours (Kendall 2008).

The goal of qualitative interviews is to supplement the information collected from the document analysis in Study 1 and to fill any gaps for missing information. Selected experts came from pharmaceutical companies that hold marketing authorisations for specific samples of innovative medicines. The interview questions were to collect information
missing from the document analysis. The interview format was flexible and was conducted in English via audio or video teleconference.

Interviewing is an important technique for collecting primary data in research, and its format can be fully structured, unstructured, or semi-structured. Fully structured or semi-structured interviews are commonly used formats, as unstructured interviews cannot generate the data that can adequately address the needs of research (Fox and Midlands 2009).

We have used a semi-structured interview as this format is more useful when researchers have some information on the research topic and want to have more in-depth information and discussion on topics that merit further investigation. This interview format allows the opportunity to probe and ask further clarifying questions (Wilson 2014).

Semi-structured interviews, like self-administered questionnaires, use a list of structured questions that are pre-defined. Semi-structured interviews, on the other hand, are led by an interviewer and require respondents to answer orally for the interviewer to record. The interview format is more adaptable and can be conducted in person, over the phone, through video conferencing, etc. In contrast, the interviewer is regarded as a technique instrument (W. M. K. Trochim 2006). In addition to the advantages of questionnaires, which must be carefully considered, the interview method has additional advantages. The interviewer can ask probing or follow-up questions.

Respondents may ask the interviewer clarifying questions. It is usually easier for the respondent because they can speak freely, which is especially useful for questionnaires that ask for opinions or have more open-ended questions. Because the interview is more
personal, it is easier to judge the quality of the answer. Response rates are considered higher. The interview method has its own limitations. These are more costly in terms of resources and time to conduct and analyse. The interviewer’s travel and time costs may need to be considered unless you are doing it virtually. increased variation due to the incorporation of the interviewer into the instrument of the technique; different interviewers may have different approaches to asking questions and engaging with respondents, which could confound comparisons (e.g., variability between different interviewers). The interviewer may ask leading questions that influence the answers given (William M.K. Trochim 2006); (Weinberg 2013).

3.4.2.1 Sample

Semi-structured interviews were conducted with the most qualified industry professionals in the pharmaceutical sector. Experts from the pharmaceutical industry who worked at the manager or above level in the marketing access function and were based in the United Kingdom were eligible. The researcher reached out to potential participants via social media platforms such as LinkedIn and Twitter, as well as through his own personal network.

In addition, a communication was sent out to potential participants in order to get in touch with them via the contact us page on the pharmaceutical companies’ homepage. When potential participants contacted the researcher by email, private messaging on social networks, or text messages, their participation was verified to ensure that they met the eligibility requirements. The researcher sent an invitation letter (Appendices 6 and 7) to all eligible prospective participants who expressed an interest in participating in the study or were referred by someone else.
The letter included additional information on the research project as well as an open invitation to communicate with the researcher about their availability to participate in an interview. This information, in addition to the email address, confirmed date, time, and location of the interview, was all recorded in a password-protected document. The name of the participant was replaced by a code.

The letter included additional information on the research project as well as an open invitation to communicate with the researcher about their availability to participate in an interview. This information, in addition to the email address, confirmed date, time, and location of the interview, was recorded in a password-protected document. A code took the place of the participant's name.

In qualitative research, the function of sampling is typically strategic and purposeful, based on who can most effectively and meaningfully answer the research questions based on specific attributes relating to the phenomena of interest, as opposed to merely representing a population in large numbers (Yardley, 2000). Smaller samples are frequently suitable for qualitative research (Marshall 1996). The objective is to describe detailed accounts of phenomena rather than to develop generalisable knowledge about successive causality. In the qualitative study, a total of 20 interviews were conducted. According to Green (2009), saturation in an interview-based study often occurs after roughly 20 interviews (Green and Thorogood 2009). As the suggestions in the literature vary, it is crucial that the researcher adopt a position and have a clear approach to determine when they will cease doing interviews. The sample size for this investigation was determined by data saturation and information redundancy. Immediate after completing each interview, the researcher took handwritten notes on key points, new material obtained from the interviews, and anything
that drew his attention (thoughts, feelings, and reflections) so that they could be used during data analysis.

The researcher continued to interview people until the interviews did not yield new information. After completing 16 interviews, the author did not develop any additional themes. To ensure data saturation, four extra interviews were performed, for a total of 20 interviews. Data saturation was viewed as a valid technique to justify the sample size.

Convenience sampling, also known as volunteer sampling, snowball sampling, purposive sampling, and theoretical sampling are all common qualitative sampling approaches. Researchers focusing on qualitative methods could employ more than one sampling strategy in their research. (Gill 2020). In qualitative study 02, the researchers chose to use the purposive and snowball-sampling methods. In qualitative research, one kind of purposeful sampling is known as the snowball technique. This method "usually happens after a study has begun and occurs when the researcher asks participants to recommend new individuals to examine," according to the definition of the snowball approach (Babar 2020).

3.4.2.2 Development of an Interview Guide

An interview guide (Appendix 8) was developed to facilitate this interview. An interview guide is comprised of a list of key topics and related questions that facilitate research involving interviews. It was made with the research questions in mind and was based on good practice guidelines (Braun & Clarke, 2013; Grbich 1999; King, Horrocks, and Brooks 2019; Ogden and Cornwell 2010). It is usually a very brief document to keep the focus on key topics without going into too many details. As it is only a guide, the interviewer can ask
questions in any order, and in some situations, it is also ok to go off script if different types of questions that were not anticipated before the interview could provide more useful information on the selected topics (Braun & Clarke, 2013). Critical and collective reflections on the results of the documentary analysis and systematic review informed the content.

Most of the questions were open-ended, positive, and written in the present tense. This was done to get a lot of good information and get people talking about the most important results of documentary analysis while giving them enough room to talk about things that were important or interesting to them. The aim of the interview guide was to obtain richly contextualised information from experts with relevant experience in the pharmaceutical industry. To do this, the interviewing process must be flexible enough so that the researcher can respond to true in-depth true experiences with unplanned or impromptu questions (Braun & Clarke, 2013).

It is believed that asking explicitly about insight and cause produces particularly rich data on these topics, particularly later in the interview (Ogden & Cornwell, 2010). Therefore, a combination of descriptive and probing questions was incorporated in a logical and funnelling manner, beginning with more general descriptive questions and advancing to more in-depth concerns.

Descriptive questions allow the participant to discuss a topic about which they are knowledgeable and enthusiastic, such as their personal experience or competence in a certain profession (Grbich, 1999). The use of these types of questions at the beginning of the interviews helped establish rapport and trust with the participant, which are essential for interactive data gathering (Braun & Clarke, 2013). Closing questions asked about goals
for the future and final thoughts. They also gave participants the opportunity to raise important topics they thought were missing from the interview and make closing comments.

The interview guide contained brief prompts for reference. If the respondent did not comprehend the question or required prompting to respond. In order to keep the interview, guide concise and easy to use during the interviews, the prompts were not exhaustively described. The researcher conducting the interviews had prior practical knowledge of the professional and organisational setting as well as the research topic, and the interviewees were all experienced marketing access professionals in the pharmaceutical industry who had a working knowledge of subject- and profession-specific terminology and employed it appropriately. Without the need for significant prompts in the interview guide, this allowed for a natural conversational interview approach with the participants.

The supervisor was presented with the draft guide. Discussions were held to find any possible flaws in the draft interview guide. The material in the updated draft guide was then tweaked in accordance with the supervisor's suggestions. The researcher went through the redrafted interview guide several times before deciding that it was ready for piloting after a final meeting with the supervisor.

A pilot interview was performed to help refine the interview guide and objectively evaluate the language, sequence, and utility. The researcher also used the pilot interview to practise interview execution and gauge the interview timeframe. Some of the question wordings in the interview guide were updated because of the pilot interview. The final version of the interview guide (Appendix 8) was used for the remaining interviews that were conducted.
The final version of the interview guide included the discussions and inquiries that are outlined in the table that can be found below. However, the structure that was described was not followed exactly during all of the interviews because an interview guide serves as a flexible instrument that directs the conversation between the interviewer and the respondent (Taylor and Lindlof 2002).

Table 4: Themes and questions covered in the final interview guide

<table>
<thead>
<tr>
<th>Introduction and Preliminary activities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Welcome and introduction</strong></td>
</tr>
<tr>
<td>A reminder about the project's history, objectives, and aims</td>
</tr>
<tr>
<td>Ask for permission to record the interview on audio.</td>
</tr>
<tr>
<td>Make sure privacy is kept (responsible management and storage of data during transcription, analysis, and reporting)</td>
</tr>
<tr>
<td>Get permission to take part.</td>
</tr>
</tbody>
</table>

Question 1 -11 are to assess timelines from licensing to Implementation of HTA recommendations

1. What is usually the Sequence to file Health Technology Assessment applications in England, Wales, and Scotland?

2. Under what circumstances would you prefer to file Health Technology Assessment application in Wales ahead of England?

3. Under what circumstances would you prefer to file Health Technology Assessment application in England ahead of Scotland?

4. Under what circumstances would you prefer to file Health Technology Assessment application in Scotland ahead of England?

5. What are the average timelines to file Health Technology Assessment applications after the approval of the licensing of medicines?

6. What factors impact HTA submission timelines following licensing of medicines?

7. Do you have any suggestions to reduce average time to file Health Technology Assessment applications after the approval of the license for medicines?

8. Are you aware of any challenges after the HTA recommendation are made available, what are the average implementation times to reimburse medicines to patients after the Health Technology Assessment recommendation is issued?

9. Are there any instances where HTA positive recommendations have not been implemented or not resulted into positive reimbursement decisions?
<table>
<thead>
<tr>
<th>Question</th>
<th>Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.</td>
<td>Do you have suggestions to reduce overall time from Health Technology Assessment Recommendation to the implementation of HTA recommendation?</td>
</tr>
<tr>
<td>11.</td>
<td>Do you have any suggestions to reduce overall time from License approval to the implementation of HTA recommendation?</td>
</tr>
</tbody>
</table>

Question 12-16 are to assess medicine usage in absence of Health Technology Assessment Recommendation or HTA recommendation as not recommended.

<table>
<thead>
<tr>
<th>Question</th>
<th>Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.</td>
<td>Are there any instances where medicines were reimbursed despite absence of HTA recommendation?</td>
</tr>
<tr>
<td>13.</td>
<td>Are there any instances where medicines were reimbursed despite receiving a negative HTA recommendation?</td>
</tr>
<tr>
<td>14.</td>
<td>In absence of HTA recommendation or negative HTA recommendation what are the key drivers of positive reimbursement decisions?</td>
</tr>
<tr>
<td>15.</td>
<td>In the absence of HTA recommendation or negative HTA recommendation, what other mechanisms have contributed to improve the patients' access to medicine in countries across the UK.</td>
</tr>
<tr>
<td>16.</td>
<td>In what situations HTA submissions are not performed, please provide the reasons for each of the following countries across UK.</td>
</tr>
</tbody>
</table>

Question 17-20 are to study differences in Health Technology Assessment Recommendation across England, Scotland & Wales?

<table>
<thead>
<tr>
<th>Question</th>
<th>Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.</td>
<td>Do you usually observe differences in Health Technology Assessment Recommendations across England, Scotland &amp; Wales?</td>
</tr>
<tr>
<td>18.</td>
<td>Are these differences in Health Technology Assessment Recommendation decreasing/increasing over time in Health Technology Assessment Recommendation across England, Scotland &amp; Wales?</td>
</tr>
<tr>
<td>19.</td>
<td>In future are these differences in Health Technology Assessment Recommendation across England, Scotland &amp; Wales likely to increase/decrease?</td>
</tr>
<tr>
<td>20.</td>
<td>What are the key drivers of differences in Health Technology Assessment Recommendations across England, Scotland &amp; Wales?</td>
</tr>
<tr>
<td>21.</td>
<td>Do you have suggestions to reduce this variability over time?</td>
</tr>
</tbody>
</table>

Question 21 to 24 are to study differences between licensing and Health Technology Assessment Recommendations on treatment availability for new innovative medicines in the UK.
22. Is the gap between licensing & HTA decisions increasing or decreasing over time?

23. In recent years have you seen any changes/initiatives in industry practices to reduce this gap?

24. Could you think of any other factors/initiatives which may positively or negatively impact the gap between licensing and Health Technology Assessment Recommendations?

25. As there are differences between licensing and Health Technology Assessment Recommendations impacting availability of innovative medicines in the UK. How would Brexit impact this situation as now responsibility for licensing of medicines has moved from EMA to MHRA?

Closing Questions

26. About access to medicines situation in UK are there any other factors that you think might be important that we have not covered?

27. What are top 3 challenges or barriers for access to medicines situation in UK.

3.4.2.3 Data collection

The interviewer administered a questionnaire over the phone or via conference call. Remote administration of the questionnaire saves money and time by eliminating the need for the interviewer to travel to meet the respondents. Telephone interviews can be held on the spur of the moment or planned in advance. Conferences or video calls, on the other hand, would require a prearranged time slot.

Because the interviewer records the responses in real time, there is a spontaneous response, but the respondent often has a limited amount of time to prepare their response. The interviewer may record their conversation with the respondents, but this would necessitate their permission as well as extra time and resources to transcribe and analyse the recordings.

Face-to-face interviews with the interviewer are the most personable option because they reinforce the interviewer's rapport with the respondent, make the respondent feel more at
ease, and allow the interviewer to observe the respondent's facial expressions and body language. Depending on the respondents' location in relation to the interviewer, the interviewer's time and travel costs can be lengthy and expensive. Respondents may have a limited period of time to formulate their responses to questions administered remotely by an interviewer, but their responses will be spontaneous. If the respondent agrees to recording the interview, it would take more time and resources to transcribe and analyse the audio data. An interviewer may administer a questionnaire to an individual or a group. Group interviews may be conducted face-to-face or remotely through conferencing and video calls. Aside from the benefits and drawbacks of interviewer-administered questionnaires, a group interview will save time by allowing a single interviewer to collect responses from different respondents. Travel time and costs may also be reduced, but more planning is likely to be necessary to find an appropriate time that meets the needs of both respondents and interviewers.

For the semi-structured interview, after evaluation of all possible methods, i.e., face-to-face interview, telephone interview, email interview, or web page interview, the researcher had decided to go ahead with an audio or video teleconference. While a face-to-face interview would have been a fair option, an audio or video teleconference was a more appropriate method. This option is more relevant in the current pandemic situation because potential interviewees were most likely working remotely, and engaging them for face-to-face interviews at their actual offices would be difficult.

At the start of the interview, the researcher made sure that the participant had understood the information on the participant information sheet and asked the participant consent verbally.
The researcher requested the permission to record the interview and the resulting audio files will be transcribed to facilitate the identification of themes. Participants were informed how the interview files and data would be stored in a password protected file using University based system which is encrypted. All paper files were stored in a locked cabinet at the University of Huddersfield. The digital files of the recordings were destroyed after the completion of the transcript and names and other identifying information were to be deleted from all electronic/paper copies of the transcript.

To conduct the interview, a participant information sheet, participant consent form, and interview guide are included in the Appendix below.

The interviewees were informed about the duration of the interview, which ranged from 45 minutes to 60 minutes. The interviews were recorded. All interview files and related data were stored in a password-protected file using an encrypted university-based system. All paper files, if any, were to be stored in a locked cabinet at the University of Huddersfield. The digital files of the recordings were to be destroyed after the completion of the transcripts and the names and other identifying information were to be deleted from all electronic and paper copies of the transcript. It was stated that the data will be used to write a report and a paper, and the results of this project will be available through an academic publication. Any information provided by participants may be quoted in publications or presentations; however, confidentiality will be maintained and any references will be anonymously quoted.
For consistency, the semi-structured interviews were done with a pre-defined checklist of questions that was used during all interviews. Depending on the expertise and interest in various topics and the flow of the conversation, the interview followed a flexible structure. This project received ethical approval from the University of Huddersfield Research Integrity and Ethics Committee (SAS-SREIC 05.05.20-2). All related aspects of confidentiality, anonymity, and informed consent were carefully considered for this project.

3.4.2.4 Data Analysis

Thematic analysis was chosen as the method to analyse the data collected. In general, thematic analysis is the most commonly used qualitative approach to analyse data collected through interviews. The theoretical positions of Braun and Clarke (2006) served as the basis for the conceptual framework of my thematic analysis of interviews. Thematic analysis is a method to identify, analyse and reporting patterns across the dataset. I chose this method because the thematic approach is rigorous and it can generate an insightful analysis that addresses specific research questions (Braun and Clarke 2006).

Furthermore, this approach complemented the research questions by allowing an investigation of the interview data from two perspectives: first, from a data-driven perspective and one focused on inductive coding; and second, from a research question perspective to see whether the data were compatible with the research questions and provided enough detail (Jugder 2016). Thematic research is adaptable to different epistemological frameworks because it is not paradigm-specific or prescriptive (Braun and Clarke 2013). It is thus a method of analysis that is compatible with a mixed-methods explanatory review in a critical realist and relativist epistemology. Other epistemological
positions can use other ways to look at qualitative data, like interpretative phenomenological analysis (Smith and Osborn 2008) are applicable to other epistemological positions.

To remain as true to the interview participants' accounts as possible, it was determined to be as consistent as possible throughout the coding process. As a result, interpretation remained entirely inductive and close to the results (Watts 2014a). To ensure that the study's results are as transferable as possible, established literature and theory can be integrated into the discussion of the research (rather than the analysis itself). This allowed the researcher to critically communicate with the analysed data without being confused or imposing his or her viewpoint on or on the shared views of the participants.

The stages of the thematic analysis approach are described in detail below.

Although these stages are in order and each builds on the one before it, analysis is usually a recursive process that involves switching back and forth between stages. These are not strict rules to follow, but rather a set of conceptual and practical "tools" that direct the study and help to promote a thorough data interrogation and interaction process. The analysis process is likely to blur some of these phases with more experience (and smaller datasets).

**Familiarisation with the data**

This step requires immersing oneself in the facts and becoming intimately acquainted with them by reading and rereading them. To prevent compromising data quality, the researcher listened to all interview tapes before they were transcribed using intelligent verbatim,
removing any irrelevant non-semantic sounds (such as "er," "mm," or "uhuh") or pauses (King et al. 2010).

The researcher transcribed and reviewed each transcript multiple times to familiarise herself in the data in order to interpret the data from the participant's perspective. As soon as possible after the interview, Microsoft Word was used to transcribe the interview with the help of field notes as needed. All transcriptions were double-checked by two different researchers for omissions, misspelled words or sentence patterns, and punctuation problems. To increase the transferability of research, a pseudo-anonymous table of participant and organisational attributes was created. At the time of transcribing, all identifying information was excluded (participant names, organisation names).

**Coding**

This stage entails creating concise labels (codes!) that mark important data features that may be key to answering the research question. It involves coding the entire data set and then collating all the codes as well as all related data extracts, for further study. For coding, the transcript documents were imported into NVivo 12. To recognise important features of the data that could be key to answering the research query, coding the data involved assigning a concise mark to parts of the transcript.

To define the main themes, problems, and meanings thoroughly and systematically within the data, the researcher coded the entire dataset using an accessible, two-level, inductive, descriptive approach in which everything of interest or significance to the research questions was coded. Watts (2014) called this a "what-how" approach (what is the
participant talking about and how is it being described?). The coding process was made to be as open and as skewed as possible with the data.

The researcher tried to be empathetic to the participants and set aside their opinions and beliefs as much as possible during the coding process, which was implemented systematically and faithfully, in order to prioritise the participants' words and viewpoints. A reflective diary was used in the process to keep track of the researcher's positionality. This was used to focus on the researcher's thoughts and feelings during each interview, as well as to make any persuasions that could have influenced data analysis. This procedure helped to make the data collection process more transparent.

To add new content, the codes were slightly changed iteratively and organically during the coding process. To address the research question, slightly overlapping codes were combined, and related codes were grouped into superordinate codes when appropriate. The aim was to create a comprehensive collection of codes that distinguishes between various concepts and ideas in the data while also capturing the patterning (Braun and Clarke 2013).

**Generating Initial Themes**

This stage entails looking through the codes and data to see whether there are any important, wider patterns of significance (potential themes). It then involves collecting data specific to each candidate theme so that you can work with it and assess its viability. Transcripts were reread after data was coded, and the codes, along with their corresponding data fragments, were re-examined to find important, wider patterns of significance in the data. The identification of patterns that reflect core organising principles
relevant to the query, rather than the frequency with which patterns occur, is the main measure of significance here.

**Review of themes**

This stage includes comparing the candidate themes to the data set to see if they tell a compelling storey about the data and address the research question. Themes are usually refined in this process, which may include splitting, combining, or discarding them. Themes are characterised as a pattern of shared meaning underpinned by a central concept or idea in our TA approach.

This meant looking at the themes to see how they fit together, if they make sense, and if there is enough evidence in the data to back them up. After that, the candidate themes were compared with the whole dataset to see if they "captured something important about the data in relation to the research question and reflected some kind of pattern or context within the dataset" (Braun and Clarke 2006). This is an active procedure in which the researcher selects how the data will be organised and structured. This emphasises the significance of the researcher’s openness and critical thinking skills. The trends that emerge should be consistent with the data and convey a tale that "rings true" with the data, from an analytical standpoint. (Braun and Clarke 2013).

**Defining and Naming Themes**

Developing a thorough overview of each theme, deciding the scope and emphasis of each theme, and determining the ‘storey’ of each are all part of this process. It also requires you to come up with a descriptive name for each theme. The candidate themes were then
further established through in-depth research that included determining their reach, boundaries, and emphasis, as well as giving them descriptive names. The most probable interpretations were chosen after exploring and evaluating possible meanings of the themes.

As a result, to stay close to the data while adding meaning to it, a primarily data-driven, semantic approach to analysis was used. The data were presented in an illustrative manner to aid in the telling of a storey about the interpreted data patterns. This entailed articulating, unpacking, and amplifying the implied meanings (Watts 2014).

Writing up

The analytic narrative and data extracts are woven together in this final step. "Data extracts were used to support an interpretation that goes beyond their particular material, to make sense of the data, and to tell the reader what it means" (Braun and Clarke 2006). It is not a good idea to use one-line qualitative extracts that are taken completely out of context. The best qualitative analyses in psychology usually show longer extracts, which are usually between 40 and 150 words long (Watts 2014b). To demonstrate the analytic point made about the data, a purposive sample relative to the established themes was drawn when selecting extracts. To keep the extract selection process as similar to the data as possible, each participant's data was re-read, and extracts that were most reflective of the participant's perspective were chosen. To avoid over selectivity, data extracts were selected from around the data to show the breadth of a theme. They were also chosen for their ability to illustrate something unique and fascinating about a subject. The themes and data
were organised in a logical order to correspond to the research questions (The University of Auckland n.d.).

3.4.3 Integration and reporting of Quantitative (Document Analysis Study 1) and Qualitative Findings (Qualitative Interviews Study 2)

There are a number of suggestions for how researchers using mixed methods should report their results. You can compare and contrast the quantitative and qualitative results, or you can mix them together and just talk about how the conclusion could be expanded (Creswell and Tashakkori 2007). Some researchers suggest using a so-called "joint display" to help with the integration of quantitative and qualitative findings (Guetterman et al. 2015). Another researcher, said that the report could be presented in order or all at once, depending on the goals and barriers. In fact, the way the results are shared will depend on a number of things, such as how important the deadlines are, who the audience is, and the rules for publishing (Bryman 2007)(Toyon 2021).

In this thesis, initially, the results of individual assessments of quantitative and qualitative data were reported in chapters 04 (quantitative) and 05 (qualitative). Findings from both the qualitative and quantitative parts were looked at to find patterns and key areas that were similar. The results of the two sets of data were compared to determine whether they agreed and in what ways they did not. Convergence was looked at in a thorough and logical way. Every time convergence and dissonance happened, it was written down. At the discussion level (see Chapter 6), the results of the quantitative and qualitative datasets were compared and integrated to give a full picture of the research goals.
Chapter 4: Document Analysis of Licensing and Health Technology Assessment Recommendations for New Innovative Medicines in the United Kingdom

In this part of the project, licencing and health technology assessment recommendations on treatment availability for newer, innovative medicines throughout the United Kingdom are being explored. This has helped to find differences between licencing and health technology assessment recommendations on treatment availability for newer innovative medicines in the UK (England, Scotland, Wales, and Northern Ireland).

4.1 Background

The landscape of medicine licencing and reimbursement in the UK is complicated. The Medicines and Healthcare Products Regulatory Agency (MHRA) and the European Medicines Agency (EMA) are the licencing bodies, and they ensure that medicines and medical devices are effective and safe. However, pricing and reimbursement matters are not within the remit of licencing bodies. Primarily, licencing approval is necessary to introduce new medicines, but it does not promise access to patients unless reimbursement recommendations are made. Due to delays in reimbursement recommendations, there is a time lag between licencing approval and medicine access for patients (Frenoy 2018). It is critical to understand the status of patient access to medicines across the UK countries following licencing approval of medicines.

The NHS adopts reimbursement recommendations based on guidance from health technology assessment bodies in the UK. While licencing recommendations are based on the safety and efficacy aspects of the medicines, HTA recommendations rely on clinical effectiveness (how the new medicine performs in clinical settings compared to the standard
of care) and cost-effectiveness (that is, if the new medicine offers better value for money).

Different mechanisms are in place to provide HTA guidance to the NHS across countries in the UK, and this could lead to confusion (Payne 2012).

The National Institute for Health and Care Excellence (NICE) in England provides guidance on the use of new and currently available medicines. The All-Wales Medicines Strategy Group (AWMSG) makes recommendations for the NHS in Wales. However, AWMSG in Wales accepts NICE guidance, and medicine is not reviewed by AWMSG if NICE considers evaluating it in the next 12 months.

Northern Ireland accepts guidance issued r by NICE or SMC, and it adopts a recommendation shortly after the recommendation is available from NICE or SMC. The Scottish Medicines Consortium (SMC) provides advice to NHS Scotland on new drug therapies and is not reliant on NICE (Payne 2012). The Health technology assessment (HTA) is used as a tool by the above-mentioned health technology assessment bodies to provide guidance for the making of pricing and reimbursement recommendations. Since HTA assessments impact pricing and reimbursement recommendations, a review of the HTA assessment outcomes is of immense value (Abbas et al. 2019).

HTA assessments could lead to recommendations such as "recommend without restrictions," "recommend with restrictions," "not recommended," or "not assessed."

"Recommended with restrictions" means that treatment of new medicines funded through public funds is limited to a subgroup of the population, contrary to a wider population covered under the approved licence (Mckendrick et al. 2017). "Recommendations without restrictions" mean that treatment will be available to all patients covered under approved
licences. "Not recommended" means that treatment will not be available to any of the patients covered under the approved licence. "Not assessed" means that the HTA assessment was not performed.

A study reviewed the licencing and reimbursement recommendations for treatment availability in five EU countries. The study results showed that 90% of all EMA-approved medicines launched between 2009 and 2016 were launched in Germany, while only 57% of the products were launched in France. In Spain, only 39% of EMA-approved medicines were available after a reimbursement recommendation was made (Mycka et al. 2019).

Another study analysed the differences between regulatory and reimbursement recommendations on treatment availability for newer medicines for six common cancers in Australia, Canada, and Europe. This study showed variability in reimbursement recommendations, resulting in inequality in medicine access across participating countries (McKendrick et al. 2017).

Relatively more medicines were assessed for reimbursement in Spain than those done by NICE in the UK. This is because multiple organisations in Spain perform HTA assessments, and these organisations have to go through a relatively lower number of steps involved in the appraisal processes. The NICE rejects more medicines because of the use of cost-effectiveness thresholds, and this leads to a not-recommended" recommendation. However, Spanish bodies largely recommend medicines with restrictive use in a subgroup of patients rather than a "not recommended" recommendation. Reimbursement recommendation timelines are better for Spanish committees, probably because of the lesser number of steps in their appraisal processes compared to NICE (Blázquez et al. 2015).
The European Federation of Pharmaceutical Industries and Associations has examined the time lag differences between licence approval and medicine access across EU countries via the "Patients Waiting to Access Innovative Therapies (Patients WAIT)" indicator. According to "The Patients Waiting to Access Innovative Therapies (Patients WAIT) Report" in 2018 (All 2019), licensing approval and medicine access varies across Europe (Northern/Western Europe: 100-200 days, Southern/Eastern Europe: 600-1000 days). A large variation in the time lag between licence approval and medicine access for patients is also observed within a country. In most countries, the rate of availability of orphan medicines is lower than all other approved products. In contrast to orphan medicines, the availability of oncology medicines is higher than that of non-oncology medicines (All 2019).

The European Commission Transparency Directive 89/105/EEC mandates national pricing and reimbursement recommendations within 120 days after the licencing approval (Flostrand et al.2014).

The results of the available studies showed disparities in the number of licenced medications commercially available in different countries. A thorough literature search revealed that there was no study evaluating the availability of medicines specifically across the UK countries. Therefore, this study aims to find differences between licencing and reimbursement recommendations on treatment availability for newer innovative medicines in UK countries (England, Scotland, Wales and Northern Ireland).
4.2 Methods

4.2.1 Research Design

This study was performed through a "document analysis" of publicly available records. The study examined new innovative medicines licenced by the European Medicines Agency (EMA) in 2017 and their subsequent assessments by health technology assessment (HTA) bodies in the United Kingdom (UK).

Information on new innovative medicines licenced by the EMA in 2017 together with all related details, i.e. date of approval, licenced indication, category of medicines (orphan and non-orphan, oncology and non-oncology), licencing approval pathway, was extracted from the EMA website (European Medicines Agency n.d.) and is included as appendix 4. Biosimilars and EMA licenced generics were excluded from the study.

The EMA is responsible for the centralised licencing procedure, which can result in a single licence valid in all EU countries. As EMA licences for innovative medicines are generally granted by the EMA, this study excluded the national licences issued by the UK licencing body, the Healthcare Products Regulatory Agency (MHRA).

The study also collected information on HTA recommendations and the date of HTA recommendations for new innovative medicines. Information was collected from the portals of the relevant HTA bodies in countries across the UK. This information on HTA bodies is listed below. The study retrieved the HTA recommendations in all UK countries from the date of licencing the medicines in 2017 until January 2020.

The National Health Service (NHS) is the publicly funded healthcare system in the UK. The NHS adopts reimbursement recommendations based on guidance from health technology
assessment bodies in the UK. Methodological details of this document analysis study have been included in Chapter 3 of this thesis.

4.2.2 Data Analysis

In this study, descriptive statistics were used to present the percentage of HTA recommendations classified as "recommend without restrictions," "recommend with restrictions," "not recommended," or "not assessed." The study results were further assessed for HTA recommendations linked to or without "managed access agreements." Recommendations were also assessed to find differences between medicines categorised as orphan vs. non-orphan, oncology vs. non-oncology, and licencing approval pathways, i.e., standard vs. non-standard. Fisher's exact test was employed for the data given in Tables 5–8 to find an association between HTA aspects and counts in different regions. A p-value of 0.05 was considered significant.

The study also recorded the time from licencing approval to HTA recommendations for medicines. Time differences between the date of licence approval and the date of HTA recommendation were calculated per medicine for each country. The maximum, minimum, mean, and median times were also identified for each country.

4.3 Results

The European Medicines Agency (EMA) approved licences for 56 new innovative medicines in 2017. From the date of licence of the medicines in 2017 until January 2020, the results of the HTA recommendations across the UK countries are summarised in Table 5. It shows that the National Institute for Health and Care Excellence (NICE) in England completed the appraisal of 28 of 56 medicines. Of these 28, 12 were "recommended without restrictions,"
14 were "recommended with restrictions," and 2 were "not recommended." The majority of NICE recommendations (i.e., 21 of 26 or 81%) were made through "managed access agreements." The Scottish Medicines Consortium (SMC) assessed 31 of the 56 medicines licenced in 2017.

Of these 31, 8 were "recommended without any restriction," 22 were "recommended with restriction," and 1 was "not recommended." All Wales Medicines Strategy Group (AWMSG) follows NICE guidance and does not review a medicine if NICE is considering assessing the particular medicine in the next 12 months. The Northern Ireland government follows the HTA guidance issued by NICE or SMC and adopts a recommendation shortly after either body has made a recommendation. In Northern Ireland, 37 recommendations were adopted based on recommendations from NICE or SMC. These 37 include 10 without restrictions, 21 with restrictions, and 6 recommendations not recommended.

Table 5: HTA assessment status of selected innovative medicines in the United Kingdom

<table>
<thead>
<tr>
<th>Overall</th>
<th>Scotland</th>
<th>England</th>
<th>Wales</th>
<th>Northern Ireland</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTA Assessments Not Performed</td>
<td>25</td>
<td>28</td>
<td>26</td>
<td>17</td>
<td>1.000</td>
</tr>
<tr>
<td>HTA Assessments Performed</td>
<td>31</td>
<td>28</td>
<td>30</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>HTA Assessments with Recommendation</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>8</td>
<td>0.147</td>
</tr>
<tr>
<td>&quot;Not Recommended&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTA recommendation (Full or Restricted)</td>
<td>30</td>
<td>26</td>
<td>27</td>
<td>31</td>
<td></td>
</tr>
</tbody>
</table>
The study results suggested that HTA recommendations were adopted for fewer licenced medicines in the UK, and this also varies between countries (Northern Ireland: 66%, Scotland: 55%, Wales: 54%, England: 50%). For most medicines, either the HTA assessment was not performed or the HTA recommendation was negative or restrictive. The results also suggested that of 56 licenced medicines, only a few were found to receive HTA recommendations without restrictions (Northern Ireland: 21%, Scotland: 22%, Wales: 15%, England: 15%).

Although the number of HTA assessments with "not recommended recommendations" was consistently low across all the UK countries, the number of "HTA recommendations with restrictions" is relatively high compared to the "HTA recommendations without restrictions." Adoption of positive HTA recommendations (with or without restrictions) varies in the UK (Northern Ireland: 55%, Scotland: 54%, Wales: 48%, England: 46%). The number of HTA recommendations without restrictions was consistently low. Additionally, the majority of positive HTA recommendations (with or without restrictions) throughout the
UK were done through "managed access agreements." "Managed access agreements" were more common in England and Wales than in Scotland.

Fisher’s exact test was employed on the data given in Tables 5–8 for finding the aspects of association between the HTA and the countries. A p-value of 0.05 was considered significant. All p values were greater than 0.05, so no association was found between the HTA aspects and the countries. As an example, detailed results of Fisher’s exact test in Table 05 are included in appendix 11 of the report.

The HTA assessment recommendations were also reviewed for the following subgroups: orphan and non-orphan medicines, oncology and non-oncology medicines, non-expedited/standard licencing approval pathways, and expedited licencing approval pathways.

**Orphan VS Non-Orphan Medicines**

For most non-orphan medicines, the HTA assessment was not completed, but for most orphan medicines, the HTA assessment was completed. Compared to non-orphan medicines, HTA recommendations for the majority of orphan medicines in England and Wales were without restrictions. In Scotland and Northern Ireland, more HTA recommendations without restrictions were observed. However, for orphan medicines in Scotland and Northern Ireland with HTA recommendations with restrictions, the number of these medicines was a little higher than the HTA recommendations without restrictions.
<table>
<thead>
<tr>
<th>Orphan</th>
<th>Scotland</th>
<th>England</th>
<th>Wales</th>
<th>Northern Ireland</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTA Assessments Not Performed</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>1.000</td>
</tr>
<tr>
<td>HTA Assessments Performed</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>HTA Assessments with the recommendation &quot;Not Recommended&quot;</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>0.258</td>
</tr>
<tr>
<td>HTA recommendation (Full or Restricted)</td>
<td>9</td>
<td>9</td>
<td>10</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>HTA recommendation &quot;Full&quot;</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>0.762</td>
</tr>
<tr>
<td>HTA recommendation &quot;Restricted&quot;</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>HTA recommendation linked with a managed access agreement</td>
<td>7</td>
<td>9</td>
<td>10</td>
<td>9</td>
<td>0.162</td>
</tr>
<tr>
<td>HTA recommendation without a managed access agreement</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Non-Orphan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTA Assessments Not Performed</td>
<td>19</td>
<td>23</td>
<td>22</td>
<td>15</td>
<td>1.000</td>
</tr>
<tr>
<td>HTA Assessments Performed</td>
<td>22</td>
<td>18</td>
<td>19</td>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>
### HTA Assessments with Recommendation

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Count</th>
<th>Count</th>
<th>Count</th>
<th>Count</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Not Recommended&quot;</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>0.942</td>
</tr>
<tr>
<td>HTA recommendation (Full or Restricted)</td>
<td>21</td>
<td>17</td>
<td>17</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>HTA recommendation &quot;Full&quot;</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>1.000</td>
</tr>
<tr>
<td>HTA recommendation &quot;Restricted&quot;</td>
<td>17</td>
<td>12</td>
<td>11</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>HTA recommendation linked with a</td>
<td>13</td>
<td>12</td>
<td>12</td>
<td>14</td>
<td>0.928</td>
</tr>
<tr>
<td>managed access agreement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTA recommendation without a</td>
<td>8</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>managed access agreement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Oncology versus Non-Oncology medicines

For most non-oncology medicines, there were no HTA assessments; however, for most oncology medicines, HTA assessments were performed. Compared to non-oncology medicines, the HTA recommendations for the majority of oncology medicines in England and Wales were without restrictions.

In Scotland and Northern Ireland, for oncology medicines compared to non-oncology medicines, relatively more HTA recommendations without restrictions were observed. However, in Scotland and Northern Ireland, HTA recommendations for oncology medicines with and without restrictions were split 50/50. For oncology medicines, nearly all HTA
recommendations (with or without restrictions) throughout the UK were made through "managed access agreements."

Table 7: HTA assessment status of cancer versus non-oncology drugs in the United Kingdom

<table>
<thead>
<tr>
<th></th>
<th>Scotland</th>
<th>England</th>
<th>Wales</th>
<th>Northern Ireland</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTA Assessments Not Performed</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1.000</td>
</tr>
<tr>
<td>HTA Assessments Performed</td>
<td>10</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>HTA Assessments with Recommendation &quot;Not Recommended&quot;</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1.000</td>
</tr>
<tr>
<td>HTA recommendation (Full or Restricted)</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>HTA recommendation &quot;Full&quot;</td>
<td>5</td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>0.714</td>
</tr>
<tr>
<td>HTA recommendation &quot; Restricted&quot;</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>HTA recommendation linked with a managed access agreement</td>
<td>9</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>1.000</td>
</tr>
<tr>
<td>HTA recommendation without a managed access agreement</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Non-Oncology

<table>
<thead>
<tr>
<th></th>
<th>Scotland</th>
<th>England</th>
<th>Wales</th>
<th>Northern Ireland</th>
</tr>
</thead>
</table>

Page | 119
Most of medicines (51 out of 56) in this review were licenced through the standard licencing approval pathway. A small number of medicines (5 out of 56) were approved through a non-standard (exceptional or conditional) pathway. The study results showed that for medicines licenced via a non-standard approval pathway, 3 out of 5 medicines received positive HTA recommendations. All HTA recommendations were made without any restrictions.

**Time from licence approval to HTA Recommendation**

The average time from licence approval to HTA recommendations varies by country in the United Kingdom. In England, the mean time was 12 months, with a range of 2 to 30 months,
and in Scotland, the mean time was 10 months, with a range of 3 to 30 months. In Wales, HTA assessments were performed locally in limited cases. This was due to the absence of NICE guidance. The mean time observed was 9 months, with a range of 5 to 11 months. This analysis was not performed for Northern Ireland as it follows the HTA guidance issued by NICE or SMC and adopts a recommendation shortly after either body has made a recommendation.

Table 8: Time from approval of the drug licence to HTA recommendation in the UK

<table>
<thead>
<tr>
<th></th>
<th>Minimum (Months)</th>
<th>Maximum (Months)</th>
<th>Mean (Months)</th>
<th>Median (Months)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scotland</td>
<td>03</td>
<td>29</td>
<td>10</td>
<td>09</td>
<td>0.166</td>
</tr>
<tr>
<td>England</td>
<td>02</td>
<td>30</td>
<td>12</td>
<td>08</td>
<td></td>
</tr>
<tr>
<td>Wales</td>
<td>05</td>
<td>11</td>
<td>09</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

4.4 Discussion

In this study, we reviewed the licencing and subsequent HTA recommendations for identical groups of EMA-licenced medicines in different parts of the United Kingdom (England, Scotland, Wales, and Northern Ireland). The study also recorded the time from licencing approval to HTA recommendations. The study results support the earlier findings about the differences in licencing and HTA recommendations and the variability of HTA recommendations in different countries in the UK and across different categories of medicines.
4.4.1 Difference between licencing and Health Technology Assessment recommendations

The study results showed that for the EMA medicines licenced in 2017, only a small number of HTA recommendations were aligned with the ‘licenced indication’. These findings were also in line with the results of a study by Mycka et al. (2019).

Variability in HTA decisions across countries

The study results show variability in the HTA recommendations across countries, which is in line with the results of the studies conducted by Mycka et al., 2019, McKendrick et al., 2017, Blázquez et al. 2015. However, the variability between countries in the UK is not as large as that observed for countries in the EU.

Variability in HTA decisions across different categories of medicines

In this study, the HTA recommendations were also reviewed for subgroups, including orphan medicines and non-orphan medicines, oncology medicines and non-oncology medicines, and non-expedited/standard pathways and expedited licencing approval pathways. The results showed that orphan medicines in the UK received more HTA recommendations than non-orphan medicines, and the majority of the HTA recommendations were without restrictions. This also predicts a better availability of orphan medicines. These results are not consistent with the earlier findings, which state that the rate of availability of orphan medicines compared to non-orphan medicines is lower across the EU countries (EFPIA 2019).

The study results showed that oncology medicines in the UK received more HTA recommendations than non-oncology medicines, and most of the HTA recommendations were without restrictions. This predicts better availability of oncology medicines. These
results are consistent with the earlier finding, which states that the rate of availability of oncology medicines is higher than that of non-oncology medicines (IQVIA 2019).

In this study, only a small number of medicines were licenced via a non-standard (exceptional or conditional) approval pathway. We find it difficult to interpret the results as the study included limited numbers of medicines licenced via a non-standard pathway. However, variability in HTA recommendations was observed in UK countries.

Managed access agreements are a common tool that public payers in European countries use to ensure early access to medicines, particularly high-cost medicines. The importance of these access schemes is likely to grow in the future (Pauwels et al. 2017). The results showed that the majority of the HTA recommendations, particularly for oncology medicines, were linked to managed access agreements.

4.4.2 Time from licence approval to HTA recommendation

The European Commission Transparency Directive 89/105/EEC mandates national pricing and reimbursement recommendations within 3 months after the licencing approval (Flostrand et al. 2014). However, in this study, the time from licence approval to reimbursement recommendation varies (2 months to 30 months) between UK countries. In fact, in the majority cases, it is longer than 3 months.

4.5 Study Limitations

This study relies on information, including publicly available licencing and HTA recommendations. While HTA recommendations are primarily a key indicator of the status of access to medicines, there are a few other mechanisms by which patients can access medicines, and these are not covered in this study. Examples of these mechanisms are
"early access schemes for medicines," "open-label extensions of the clinical studies," and the "availability of the medicines in response to individual patient requests."

4.6 Conclusions

After the licencing of innovative medicines, the adoption of HTA recommendations is low and varies in the UK countries. The number of HTA assessments that resulted in a "not recommended" recommendation was consistently low across all UK countries. However, the number of "recommendations with restrictions" is relatively high compared to that of "recommendations without restrictions." Most of the positive HTA recommendations across the UK were contingent upon managed access agreements.
Chapter 5: A qualitative analysis exploring access to medicines situation in United Kingdom

5.1 Introduction

Study 02 is qualitative research using semi-structured interviews with relevant experts to project the access to medicines situation in the United Kingdom. As previously discussed in Chapter 3, our overall research is an example of an explanatory design follow-up explanation model. The follow-up explanations model is used when a researcher needs qualitative data to explain or expand on quantitative results (Cresswell et al., 2003). In study 01, quantitative data was collected, and its results were reported in Chapter 04; this was followed by the collection and analysis of qualitative data in study 2, and the results are reported in this chapter 5. The quantitative part takes priority in the explanatory design follow-up explanation model and is followed by the qualitative part.

Methodological details of this qualitative study, which include sampling, interview guide development, data collection, and data analysis techniques, have been included in Chapter 3 of this thesis. This chapter states the aims and objectives of the qualitative study, followed by the results of the study.

Aims and objectives:

The aim of this research was to evaluate the access to medicines situation in the UK.

The key objectives of this research are listed below. The interview questions were framed in accordance with the objectives of the study.

- To study timelines from licencing to reimbursement of medicines
• To study the gap between licencing and health technology assessment recommendations on treatment availability for new innovative medicines in the UK.

• To study differences and variability in health technology assessment recommendations across countries in the UK.

• To investigate post-licensing medicine uptake and/or health technology assessment recommendations.

• To identify key challenges or barriers for access to medicines in the UK.

Based on twenty interviews, the qualitative study's data analysis led to the development of six overarching themes and several subthemes (Table 9). The findings within each theme are discussed separately, but were frequently interwoven during the interviews.

My thematic analysis of interview data was grounded in the theoretical stances of Braun and Clarke (2006). Patterns in a data set can be discovered, analysed, and reported using a technique called "thematic analysis." The selection of thematic analysis as an appropriate method for analysing qualitative data is also influenced by the objectives and aims of the study (Smith and Firth 2011). The thematic approach appealed to me since it is methodologically sound and can yield fruitful analysis that responds to well-defined research questions (Braun and Clarke 2006).

Furthermore, this data analysis approach complemented the research questions by enabling an investigation of the interview data from two perspectives: first, from a data-driven perspective and one focused on inductive coding; and second, from a research question perspective to see whether the data were compatible with the research questions and provided enough detail (Jugder 2016). Thematic research is adaptable to different
epistemological frameworks because it is not paradigm-specific or prescriptive (Braun and Clarke 2013). Consequently, this method of analysis is consistent with a mixed methodology explanatory review in a realist and relativist critical epistemology. Other epistemological viewpoints are compatible with other qualitative data analysis methodologies, such as interpretive phenomenological analysis (Smith and Osborn 2008).

5.2 Results

This section provides information about the demographics of the participants, followed by the results of the study.

In total, 62 professionals were approached to participate in this study, 20 agreeing to do so. In total, 20 interviews were conducted. The ratio of males to females was nearly even, with 52% of males and 48% of females making up the total population. The duration of each interview was around one hour.

Table 9: Characteristics of the Participants

<table>
<thead>
<tr>
<th>ID</th>
<th>Gender</th>
<th>Job Title</th>
<th>Length of interview</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interviewee 1</td>
<td>Female</td>
<td>Director, Global Pricing and Market Access</td>
<td>61 minutes</td>
</tr>
<tr>
<td>Interviewee 2</td>
<td>Male</td>
<td>Health Economics, Market Access, and Reimbursement Lead</td>
<td>61 minutes</td>
</tr>
<tr>
<td>Interviewee 3</td>
<td>Male</td>
<td>Senior Director, Market Access UK&amp;I</td>
<td>67 minutes</td>
</tr>
<tr>
<td>Interviewee</td>
<td>Gender</td>
<td>Title/Position</td>
<td>Duration</td>
</tr>
<tr>
<td>-------------</td>
<td>--------</td>
<td>---------------</td>
<td>----------</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>Pricing &amp; Market Access Associate Director UK &amp; Ireland</td>
<td>55 minutes</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>Global pricing implementation lead</td>
<td>59 minutes</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>Associate Director Health Economics Outcomes Research</td>
<td>55 minutes</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>Team Lead - HTA &amp; Outcomes Research, Associate Director</td>
<td>61 minutes</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>Senior National Market Access Manager (UK &amp; Ireland)</td>
<td>60 minutes</td>
</tr>
<tr>
<td>9</td>
<td>Male</td>
<td>Senior HTA and OR Manager</td>
<td>66 minutes</td>
</tr>
<tr>
<td>10</td>
<td>Female</td>
<td>Manager, Market Access</td>
<td>52 minutes</td>
</tr>
<tr>
<td>11</td>
<td>Female</td>
<td>Market Access Manager</td>
<td>62 minutes</td>
</tr>
<tr>
<td>12</td>
<td>Female</td>
<td>Health Economics Manager</td>
<td>64 minutes</td>
</tr>
<tr>
<td>Interviewee</td>
<td>Gender</td>
<td>Role</td>
<td>Duration</td>
</tr>
<tr>
<td>-------------</td>
<td>--------</td>
<td>------</td>
<td>----------</td>
</tr>
<tr>
<td>13</td>
<td>Male</td>
<td>Market Access Solutions Lead</td>
<td>65 minutes</td>
</tr>
<tr>
<td>14</td>
<td>Male</td>
<td>Head of Market Access UK</td>
<td>58 minutes</td>
</tr>
<tr>
<td>15</td>
<td>Male</td>
<td>Head of Access &amp; Pricing, UK (Innovative Medicines)</td>
<td>68 minutes</td>
</tr>
<tr>
<td>16</td>
<td>Female</td>
<td>HEOR Team Lead</td>
<td>56 minutes</td>
</tr>
<tr>
<td>17</td>
<td>Male</td>
<td>National Market Access Lead</td>
<td>53 minutes</td>
</tr>
<tr>
<td>18</td>
<td>Male</td>
<td>Associate Director</td>
<td>Int'l. Market Access</td>
</tr>
<tr>
<td>19</td>
<td>Male</td>
<td>Head of Access and Value</td>
<td>53 minutes</td>
</tr>
<tr>
<td>20</td>
<td>Female</td>
<td>Health Economics Outcomes Research Market Access Lead</td>
<td>53 minutes</td>
</tr>
</tbody>
</table>

Overall thematic structure

The following table lists the main themes and subthemes that emerged during the interviews and after transcribing the data.
<table>
<thead>
<tr>
<th>Themes</th>
<th>Subthemes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time Lag between Licencing to Reimbursement</strong></td>
<td>• Time lag from licencing to HTA application submissions</td>
</tr>
<tr>
<td></td>
<td>• Time lag from HTA application submission to HTA recommendation</td>
</tr>
<tr>
<td></td>
<td>• Time lag from HTA recommendation to reimbursement</td>
</tr>
<tr>
<td></td>
<td>• Trend for Time Lag Between Licencing and reimbursement</td>
</tr>
<tr>
<td></td>
<td>• Suggestions to reduce the time lag between licensing and reimbursement</td>
</tr>
<tr>
<td><strong>Gap between licensing and reimbursement of medicines</strong></td>
<td>• Key drivers of the gap between the licencing and reimbursement of medicines</td>
</tr>
<tr>
<td></td>
<td>• Trend in Gap between Licencing and reimbursement of medicines</td>
</tr>
<tr>
<td></td>
<td>• Suggestion to decrease the gap between drug licencing and reimbursement</td>
</tr>
<tr>
<td><strong>Variability in HTA recommendation/Reimbursement across countries in UK</strong></td>
<td>• Key drivers of variability in HTA recommendation/reimbursement across countries in UK</td>
</tr>
<tr>
<td></td>
<td>• Trend for variability in HTA recommendation/reimbursement across countries in UK</td>
</tr>
<tr>
<td></td>
<td>• Suggestions to decrease the variability in HTA recommendation/reimbursement across countries in UK</td>
</tr>
<tr>
<td>Impact of Brexit on access to medicines</td>
<td>Medicine uptake</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>• Shift in regulatory responsibilities from EMA to MHRA</td>
<td>• Medicines uptake post HTA recommendation</td>
</tr>
<tr>
<td>o Resources impact</td>
<td>o Implementation timelines and delays</td>
</tr>
<tr>
<td>o Sequence of a licencing application filing sequence</td>
<td>o Implementation challenges</td>
</tr>
<tr>
<td>▪ Risks and opportunities</td>
<td>o Suggestions to improve medicine uptake</td>
</tr>
<tr>
<td>o Gap between licensing and reimbursement</td>
<td>• Medicines uptake without HTA recommendation/ negative HTA recommendation</td>
</tr>
<tr>
<td>o MHRA new working model (collaboration with other regulators e.g., Reliance, project Orbis)</td>
<td>o HTA is the gatekeeper for routine commissioning</td>
</tr>
<tr>
<td>• Early and closer collaboration between regulatory, HTA bodies and payers e.g., ILAP, EAMS</td>
<td>o Reasons for the absence of HTA recommendations</td>
</tr>
<tr>
<td>• Drive to bring the medicines earlier in UK than in EU</td>
<td>▪ NICE remit/capacity to review all medicines</td>
</tr>
<tr>
<td>• Parallel trading market</td>
<td></td>
</tr>
</tbody>
</table>
Historically there are some categories of drugs that do not have to go through HTA process e.g. HIV treatments.

- HTA bodies fees
  - Medicine uptake mechanisms in the absence of HTA recommendations/negative HTA recommendations
    - Interim funding e.g. CDF & IMF
    - Clinical commissioning agreement, value-based agreements, value-based partnerships, national agreement with NHS rather than with NICE, or agreements at local level
  - Individual funding requests
  - Private Insurance

<table>
<thead>
<tr>
<th>Access to Medicines Challenges in UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>• NICE HTA process/methodology capacity to appraise and assign appropriate value to all categories of medicines.</td>
</tr>
<tr>
<td>o Strict reimbursement criteria/lack of flexibility in HTA system particularly around incremental cost-effectiveness ratio (ICER) thresholds</td>
</tr>
<tr>
<td>o HTA process evaluation timelines</td>
</tr>
<tr>
<td>o Risk averse nature of system/Unwillingness of NICE committees to make decision in face of uncertainty.</td>
</tr>
<tr>
<td>o Labour intensive/ Costly</td>
</tr>
</tbody>
</table>
- Cost per QALY mechanism

- Pricing of medicines
  - High-tech medicines pricing challenge
  - Complex value-based pricing schemes

- Data Packages
  - Less mature data
  - Requirement of long-term data
  - Divergent requirements of HTA bodies
  - Evidence generation for rare diseases/ultra-rare diseases

- Transition after Brexit
  - Uncertainty of the regulatory process
  - Harmonization of regulatory procedures
  - Risk of delay in licence filing

- Pharmaceutical spending Budget
  - Covid impact
  - Budgetary implications in Scotland
  - Underfunded NHS
  - Affordability & transactability

- Human capacity and resourcing

- Lack of the capacity of healthcare system for the uptake of medicines
  - Precision medicines
| o Infrastructure/specialist services to administer |
| o Local Adoption |
| o Lack of well-defined clinical pathways |
| o Delays in implementation/infrastructure/specialist services to administer |
| o Hurdle for non-cancer drugs |

- Market access decisions are made at above country level.
- Non uniformity in decision making
- To establish UK as the centre of innovation and access
- Quality of the trials and trial data and having the right endpoints
- Digital Healthcare
Figure 7: Thematic Map
The results of each of the above-mentioned themes are shown in detail below, one theme at a time. Sometimes, subthemes are built into each main theme, but they are not labelled as section headings to aid the narrative's general flow.

5.2.1 Time lag between licensing to reimbursement

Although there are multiple interrelated factors that impact the access to medicines situation in a country, the time lag between licensing and reimbursement following HTA recommendation is an important matrix of this study. Interview participants were asked questions about the time gap between licensing and reimbursement. The responses of the interview participants were categorized under three different time lags. The first time lag was from licencing to HTA application submissions. The second time lag was from the submission of the HTA application to HTA recommendation. The third time lag was from HTA recommendation to reimbursement.

**Time lag from Licencing to HTA application submissions**

Qualitative data has suggested that historically the standard practice was to file the HTA application after license approval. However, there are now provisions to file HTA application to some HTA bodies, e.g., HTA submissions to NICE, before licence approval.

For the majority of the appraisals, you submit to NICE 9 to 12 months before license and one year later you submit to SMC. [P-FT]

One example is Astra Zeneca product calequence [P-TH] [AN: Calequence NICE submission was completed on 10th August 2020 which was before license approval date i.e., 05 November 2020 and NICE recommendation was published on 21 April 2021].

I worked on a product called brentuximab vedotin where we did both at the same time and then we received positive regulatory approval from EMA and then we received the NICE decision the following week…. For non-oncology medicines they don’t have that benefit, you have to wait till you get positive regulatory results before you actually have to submit to NICE and with oncology a lot faster in that sense. [P-MJ]
The United Kingdom’s Pharma Scan Horizon scanning process has enabled early engagement and this HTA submission even before the license. This scoping exercise is conducted before a product has received a licence and before a product is referred for appraisal to NICE.

*So, the manufacturers are kind of obliged to give this data to the horizon scanning to prepare the NHS to prepare for certain innovations.* [P-FT]

*They will have access to horizon scanning databases which will give them an indication of what’s coming up.* [P-FF]

**Reasons for Absence or Long Delays of HTA submissions**

Although HTA recommendations play a key role for access to medicines, absence or long delays of HTA submissions have been observed. Qualitative data suggest multiple reasons for absence or long delays in HTA submissions. These reasons could be lack of mature data, HTA bodies’ requirements for long-term data, clinical trial didn’t do well, HTA bodies back logs, resource constraints both at HTA bodies and pharmaceutical companies, commercial viability, pricing or cost considerations, incremental drug discovery and treatments not eligible for HTA etc.

Participants were of the view that due to expedited regulatory pathways, medicines are being licenced based on relatively immature data, which could not be considered robust to get approvals from HTA bodies.

*So, you could get a license based on relatively immature data, not very mature survival data, and you've met your primary end point of an intermediate, like PFS or something that could be sufficient for you to get even earlier licensing based on this kind of pathway. But it may not be feasible for NICE and there may be too much uncertainty in your economic model.* [P-FF]

Participants highlighted the HTA requirement for long-term data as one of the reasons for absence or long delays in HTA submissions.
Another key challenge that we have, and it’s been faced in Nice, is that we’re always being asked for longer term data. So the CDF was used or the new Innovative Medicines Fund is around that, like giving you access quickly enough when you don’t have the longer term data. When Nice says long term data, they don't mean like two years or five years. They mean ten years or 30 years. And then we just start to think, whilst it’s very important from a decision point of view, it’s frankly not realistic to run a clinical trial for five years or ten years or 30 years when it comes to like acute conditions. So that’s something else that needs to change. There needs to be a balance between how you assess uncertainty and how you’re able to quantify it and be able to make accountable decision with the amount of uncertainty still remaining. [P-DN]

For HTA submission, the key driver is always the long-term data. [P-TH]

There are situations where the clinical trial didn’t go so well, and you need more information to continue forward with the regulatory procedure, you may have to wait. Perhaps the quality of the data was not what was expected, and as a result, the HTA submission is delayed.

Sometimes maybe the clinical trial didn’t do so well, like in the case of oncology medicines perhaps NICE has scheduled for this submission to happen, and while the regulatory process is very early in the stages, and then you still waiting for more data and perhaps the data was not as positive as you thought it would be, and therefore this submission is suspended. [P-MJ]

Sometimes, companies opt to enter a data collection arrangement with HTA bodies/payers while they wait for data that is acceptable enough for positive HTA recommendation. This results in the absence or delay of HTA submissions.

A company could be waiting for a better data to get another year of another year of overall survival. If it’s oncology to support their submission. It could be that the company themselves have decided that they don't see a route forward, so they withdraw from the process and in that case, NICE would usually issue a negative guidance on the basis of no submission. [P-AK]

Sometimes, companies opt not to submit an HTA application because the product is not regarded commercially feasible, which could be the result of a relatively small market.

There are a few considerations that this discrepancy might come from, and probably it’s the commercial, whether it is commercially viable. [P-DN]
In terms of absence of HTA submissions... It may be that some of them relate to, you know, small markets, like rare diseases where the companies involved have maybe had initial conversations and thought it’s not worth it. [P-PM]

The submission of an HTA application is a resource-intensive endeavour. Sometimes, companies struggle to file the HTA application due to resource constraints.

Any last-minute questions from regulators or other ongoing HTA submissions have downstream impact on the HTA submission package. [TH]

HTA bodies have a backlog due to a large number of HTA submissions. This has become more substantial as a result of the attention of HTA bodies to pandemic-related initiatives and an increase in the number of products eligible for HTA evaluations.

NICE has a huge backlog right now. Absolutely huge because they paused all operations basically for dealing with pandemic related projects. [P-MR]

At the moment the SMC’s backlog is quite significant, even if you were to proactively indicate you were submitting kind of on or around license point of license, it’s very unlikely that there will be at least a three-to-six-month delay in terms of the actual slot that you get or your submission so that it’s affecting access timelines for SMC at the moment. [P-FF]

Another key reason for backlog at NICE is due to recent agreement between the Association of British Pharmaceutical Industry and NICE. Per this agreement, NICE has commitment to review all new treatments which was not the case in the past.

Backlog still hasn’t been cleared and that goes with a commitment in the latest agreement with ABPI to review every new indication, whereas NICE didn’t have that in the past. So, reviewing every indication in the past wasn’t something that NICE said they had to do and that would be some of why you wouldn’t have holes in HTA is because there wasn’t that commitment in the past. [P-MR]

HTA submissions are sometimes prioritised for other nations, such as Germany, over the United Kingdom. This causes a delay in HTA submissions to UK HTA bodies.

From a timing point of view in EU the UK may start its HTA process first but generally... most companies would prioritize getting a final price agreed in Germany before going through an almost any other European HTA assessment. So, Germany is normally prioritized. UK maybe as a close second or very much in line. [P-AK]
Pharmaceutical companies when considering developing products in multiple indications take into account the timing and sequence of HTA submissions as this could impact the price of the product positively or negatively.

*Pharma companies are worried because they have multi-indication and medicines but not all of them are equally valuable. And if you happen to submit early on for an indication where the pricing for an indication is likely to be very low...... it means that for your future indications, you've now jeopardized that before even started. [P-MJ]*

There are situations where products are not considered eligible to go through the evaluation procedure with HTA bodies. When this happens, companies have the option of going directly to payers or regional or local health bodies.

*In case NICE has not selected your product for evaluation, you can just go straight to NHS England really and discuss commissioning with NHS England and you can get it on GP prescribing systems and things like that so. it. It then becomes down to local GP budgets and whether they want to add at CCG or an ICS level. [P-PM]*

There are times when a pharmaceutical company's internal evaluation shows that the product does not meet the cost-effectiveness criteria. In these cases, the company decides not to submit the HTA because it would receive a negative recommendation from the HTA body.

*One example maybe without mentioning that drug itself and the condition I've worked on. We decided not to submit because we thought we couldn't prove it to be cost effective. [P-SR]*

In some cases, drug discovery is considered incremental as new treatment show only trivial improvement. So, when this happens, companies decide not to hurry up their HTA submissions.

*The reality is that most drug discovery is kind of incremental. You're showing trivial improvements, every time a new treatment comes out, and I think, well, if that's the case there's no incentive to increase the speed of time. It all comes down to the value I think if.*
And pharma companies should come up with treatments that you know significantly improve patients’ lives to the point where they don’t need other treatments. [P-NP]

Drivers of HTA Application Submissions

The submission of HTA applications and sequence of HTA submission to various HTA bodies is driven by multiple factors.

Pharmaceutical companies sometimes make a strategic decision, based on a number of factors, to put submissions in other countries ahead of HTA submissions in the UK.

There could be strategic decisions taken to focus on FDA and EMA 1st and then bring in to MHRA later. Even if the burden on putting in the applications isn’t as great. [P-FF]

It’s a growing challenge in the UK and the requirements for NICE are very stringent and it’s a tough barrier to act to enter in the UK market. So, there can sometimes be strategic decisions from pharmaceutical companies to not submit. [P-FF]

In some cases, companies may prioritise submissions in one country to put political pressure on a neighbouring country to expedite access to medicines.

If you’re likely to get SMC approval and you know that NICE is going to be very challenging. You may decide that you want to go SMC first, get the approval and then use that to apply political pressure and use you know inequitable access kind of argument to have an influence on NICE. [P-FF]

For Orkambi® we decided to strategically go to Scotland first because reimbursement in Scotland first creates some sort of inequality of access. So, people in in Scotland get access to a very important medicine which put pressure on England to do something about that. [P-TH]

The United Kingdom is one of the few countries in the world to place HTA submissions at the top of the list. This is because pricing and access decisions in many countries are based on the UK as a reference country.

Because the UK is a cost effectiveness market, and a lot of countries would tend to pick up the UK as a reference. In that case, they just don’t want to file in the UK first because they know that the product is never going to be cost effective and is not going to be recommended. For example, if you know that you’re not going to compromise on price and the product will be not cost effective, it will not be recommended by NICE then. [P-TH]
Sequence of HTA Application Submissions

The United Kingdom is among the first few countries where the HTA process is prioritised. With regards to sequence of HTA submissions in UK usually there is staggered HTA filing approach, i.e., usually filing to NICE comes first and then to SMC. These HTA filing sequence decisions are driven by NICE influence on reimbursement decisions in other countries around the world, size of the market, NICE flexibility to allow submissions earlier than licence approval.

In some situations, NICE and SMC submissions are done in parallel. There are also some situations where the submission of HTA is made to SMC first and to NICE later. AWMSG in Wales usually follows the NICE recommendations. However, in some situations HTA submissions can be made to AWMSG e.g where NICE submission is uncertain, not allowed or is delayed for long time.

From a timing point of view in EU the UK may start its HTA process first but generally I would say that most companies would prioritize getting a final price agreed in Germany before going through an almost any other European HTA assessment. [P-AK]

HTA filing decisions are driven by company objectives, size of the commercial opportunity, and political pressures due to early access decisions in other countries.

HTA submissions sequence depends on what the company’s objectives are like they might look at the target population or whether there’s a market in those countries, so you know when it comes to rare diseases. For example, they might find that there are very few patients in Scotland who have that condition, and therefore here’s not much benefit to the company to submit. [P-SDS]

In UK, usually there is staggered approach, i.e., filing to NICE comes first and then to SMC.

I would say that filing to NICE is always considered the priority. It’s normally one of the first globally, not necessarily even in just the UK and because for the SMC for Scotland you can only file once you have a positive CHMP opinion that’s kind of the trigger for filing for Scotland. So, the order is kind of NICE and then kind of six months later, Scotland. [P-KN]
The decisions made by the England HTA body, known as NICE, are not just adhered to in Wales and Northern Ireland; they also have an impact on market access decisions made in nations outside of the UK.

*NICE as I mentioned is influential in other market as well, so getting that across the NICE would be very beneficial for countries like. Slovakia Greece. Canada, Australia. These are also big markets, but again it varies from drug to drug of course and condition to condition but they really refer NICE.* [P-SR]

*So, if you want HTA recommendation in the UK. For England it is NICE and in Scotland is SMC, so you have to file it separately. AWMSG in Wales sometimes it follows NICE, sometimes you have to do application there and then you don't file in Northern Ireland.* [P-VS]

Although HTA submissions can be made to NICE even before the outcome of a marketing authorization application, for SMC submissions, you have to wait for the CHMP opinion.

*In terms of HTA submission timeline, I think SMC still prefers If you get CHMP opinion first. I don't have this sense that is going to change. The most recent SMC submission I did was probably last year August and we had to wait until we have CHMP opinion and then we had to submit to SMC.* [P-MJ]

Sometimes, HTA submissions to NICE and SMC are handled in parallel.

*We have a HTA submission plan for this January with NICE and we are planning for actually a parallel submission with SMC at the same time.* [P-SK]

Sometimes, HTA submissions to SMC are earlier than NICE. This is an option when the company anticipates NICE submission difficult and there is a desire to have a faster HTA recommendation from any UK HTA body e.g., SMC.

*And one reason that I may think of is that SMC is slightly faster. I would say in terms of their decision and then so if the company would like to have a reference from UK HTA body faster so they can go through SMC.* [P-NL]

*Now if there are specific challenges with NICE that you're unlikely to be able to overcome before you submit, and therefore you take a strategic decision to delay. That you could make a case to submit earlier for SMC while you're waiting for that. One of the reasons for that is SMC tend to be a little bit more flexible in their approach and a bit more pragmatic.* [P-FF]
For certain treatments, the SMC process offers flexibilities that NICE would not offer.

Typically, the Patient and Clinician Engagement (PACE) process is used to support the SMC assessment of end-of-life and orphan drugs. SMC also has modifiers that provide flexibility in decision-making for orphan medicines.

SMC also have this additional process called PACE, which takes into account modifiers for your disease. So, for example, if it’s end of life or if it’s a rare disease then you might be able to, for example, demonstrate cost effectiveness under those parameters in a way that you may not be able to do for NICE. [P-FF]

The Scotland ultra-orphan process is considered more flexible for certain types of medicines e.g treatments for rare diseases.

So, if that companies with rare drugs they might choose to go to Scotland first because they’ve got this new ultra-orphan process which is seen as more flexible for certain types of drugs. [P-ALS]

Companies may file with the AWMSG of Wales in the absence of NICE submissions, such as when HIV drugs are not evaluated by NICE, or when there is a delay in submitting to NICE or when the submission package is not as robust as NICE requires.

NICE is still selective. They’ve improved, they’ve broadened the number that they would be appraising. I mean, it’s still a selective process that you have to go through in order to be appraised. I think also in addition to that will be the availability of data as well, perhaps the company might make a decision or a strategic decision that maybe just not ready for NICE. Then they decide to move ahead with an AWMSG. [P-CD]

In some exceptional cases, if there are delays to a NICE submission, then you can put in a separate submission to AWMSG and you can get a separate approval, but it’s a rare exception. It’s not usually the standard practice. [P-FF]

There are situations where companies receive a negative recommendation from NICE and wanted to explore if AWMSG would accept a submission.

I guess if you had a not recommended from NICE, you could approach the AWMSG to see if they would be interested in doing a review and or. I know there’s been occasions for kind of paediatric indications where it's going to AWMSG individually. [P-KN]
When NICE cannot agree on a submission date, companies sometimes think about filing with AWMSG. This could put pressure on NICE. Also, AWMSG encourages companies to think about filing with them, and it does not take as many resources as NICE, so it might be better for smaller companies.

As a company you could only really use AWMSG for a reason. NICE is not giving you a date to submit, and we want to put pressure on it or because NICE would not be appraising those drugs. AWMSG do try to encourage us and they have regular meetings with the industry and they do raise the merits of going with AWMSG if you’re in between processes and you haven’t really secured a NICE date yet, that’s probably more applicable for smaller companies, which cannot be as agile or have the resources to wrap things up as quickly as big pharma companies. [P-DN]

The reason I can think of is for example we have license extensions. Another reason could be cost itself, the resource element as well so and in terms of the market is very small. Because it’s not important or big market itself and they don’t have the resources, but at the same time they think that having something as a proper formal appraisal of HTA might be very useful, and that’s where they can go to AWMSG. [P-SR]

The HTA assessment is not performed in Northern Ireland. They refer mainly to NICE recommendations and to the SMC recommendations in some cases.

So, it can be quite unclear in Northern Ireland, and I think sometimes they follow the SMC guidance as well. Yeah, so it can be unclear whether they follow the NICE guidance or the SMC, and I’ve got no particular experience in Northern Ireland, but I have heard that it’s going to become even more complicated with Brexit. [P-KN]

**Time Lag from HTA Application Submission to HTA recommendation**

This time lag begins with the commencement of the HTA process and continues through the length of the HTA process and the time it takes for a HTA recommendation. While the HTA review process is well defined, review timelines vary depending on the type of submission. The NICE fast track appraisal takes approximately 6 to 9 months, but the conventional route takes around 12 months to 2 years, depending on the number of committee meetings that took place. The SMC evaluation time is faster. Although submission to SMC is usually
completed after NICE, SMC HTA recommendations are expected to be available close to
NICE recommendation, as SMC HTA evaluation is faster.

_We got very defined timelines from the time of submission to NICE final decision. Delay
comes only on your submission date. But from the moment you’ve submitted, it’s actually
quite defined. usually, the process takes about anywhere between I would say 7 to 9 months
and it’s quite clearly well laid out process._ [P-SK]

NICE Fast track appraisal reduces the time lag to approximately 6 to 9 months. While the
conventional route takes around 12 to 18 months and can go up to 2 years.

_One of the things that we have seen is that NICE is offering the fast-track appraisal basically
one way to ensure, the process for submission to funding is reduced by approximately I would
say six months and that means one committee meeting would be needed. The FAD would be
published earlier, and the funding because of the technology appraisal guidance otherwise
called tag it would be within 30 days as opposed to 90 days. So, technologies that they have
went through the fast-track appraisal from the license to the reimbursement we are talking
approximately 6 to 9 months._ [P-FT]

_So, if you look about other therapies that they went through the conventional route and
some of them they have taken at two committee meetings, and I would say this this time lag
could easily be doubled between let’s say 12 and 18 months to two years._ [P-FT]

The SMC evaluation time is relatively faster, which is due to relatively less stringent
requirements compared to NICE. In SMC since everything is done in-house, results appear to
be more consistent. Although in NICE work is outsourced to different evidence review
groups and committees, therefore outcomes do not appear to be consistent, and they are
less predictable.

_SMC has less stringent requirements around evidence, and particularly around cost
effectiveness. so that generally comes faster._ [P-TJ]

_NICE have different standards as they have different evidence review groups. There are some
evidence review groups that are very good, and they know exactly what’s going on. But there
are some that are, not so good and you end up having submissions that were either handled
really well or the way it handled really well depend on the evidence review group. I think this
is why SMC has done really well because SMC is all in house. While NICE aims to be consistent
in the decision making because they’re not using consistent bodies to assess, you might find
that two appraisals might get two different outcomes. NICE has four committees, and
between four committees I think consistency is really key._ [P-MJ]
The SMC abbreviated submission process is for medicines which are nearly similar to already available treatments and have kind of the same benefit and cost range.

*I have heard of the SMC doing an abbreviated submission process which is for a drug that’s very similar to other drugs. Similar cost, similar benefits. So, we just do a cost minimisation approach. Because we don’t require a full economic model, it’s just an abbreviated submission, and it doesn’t go to a full committee meeting. Because it’s a shorter submission, less resource is required from the HTA body as well. [P-ALS]*

Post COVID virtual meetings culture has helped to accelerate the HTA evaluation process as various meetings that previously require face to face attendance now can be done relatively quickly when conducted virtually.

*One thing due to Covid, so you know the SMC and NICE they’re all meeting virtually. Which has speed things up, because when the committees used to meet face to face, you had to have a particular a minimum number of members on the committee. Depending on the time of year, people are on holiday, it’s very difficult to get people to travel to the officers and sometimes committee meetings had to be cancelled because they didn’t have enough. committee meetings, whereas since, COVID and virtual committee meetings. I’ve heard from my ex-colleagues at NICE that hasn’t happened. It’s been a lot easier to have quorum at committee meetings. [P-ALS]*

**Time Lag from HTA recommendation to reimbursement**

This is the amount of time it takes for a favourable HTA recommendation to become a funding decision and then implemented. Qualitative data suggests that NICE recommendations are required to be implemented in 90 days (30 calendar days for Fast Track Appraisals). For oncology medicines, implementation is usually immediate, that is, between 0 and 30 days.

*Once NICE approves, NHS has to implement with in certain period, but it doesn’t mean to say that you know each trust will get there as fast as the others, whereas for oncology we’re very lucky in the sense that everything is funded centrally through NHS England. So, between when NICE says yes, it’s a 30–90-day allowance period for hospitals and trust to be able to implement it. In that time, it’s funded by NHS England. So, there are no delay in between*
getting the yes from NICE and actually implementing it, so it’s accessible to patients pretty much from day one. when NICE says yes, there is funding in place for oncology medicines, so I think the challenge might be more for non-oncology space. For oncology specifically it is just the typical things which is uptake at Physician level. [P-MJ]

While aim is to implement within stated timelines, there can be delays in implementation, e.g. some treatments require additional nurse time or facilities to administer.

But the legal component of a NICE positive recommendation is implementation within 90 days. So that is generally the aim of, you know local CCG’s and health bodies to try to implement within that timeline. However, they can run into two issues within the service like practical issues, so if you can, if you can think of like any practical issues, for example, like if you’re administering a drug that’s intravenous, when you’ve, primarily focused on pills in that service for example. Then you might need additional nurse time, or you might need additional facilities to kind of implement that. Or you know if so, if there’s an administrative burden to the to the product, then that can result in a bit of a delay to try and you know, acquire those additional resources. [P-FF]

The Scotland SMC recommendation is not legally binding and there are not defined implementation timelines, so it is just SMC advice, and then it is up to the health boards in Scotland to decide when to implement and whether they want to reimburse the medicine. It could take 30 days for SMC recommendation to be implemented at the health board levels. Sometime there may be delays in implementation as some guidelines need to be updated at the health board level prior to implementation.

The Scotland SMC recommendation is not legally binding, so it’s just it’s just SMC advice, and then it’s up to the health boards in Scotland to decide whether they want to reimburse the medicine. [P-SDS]

SMC have a very good network of trust, and the information pretty much gets cascaded up quite quickly. I don’t believe it’s centrally funded like NHS England is, but they have very good network where the information is passed on very quickly and they opted that guideline, but there is a lag in that third degree where different trust has to update their guidelines and, in that sense, I suppose there can be delays so it’s not centralized as England and so there could be a lag. But from my experience, I think SMC is very good at the network and information sharing to ensure that it gets it a trust level. Once medicine that has been approved by SMC, they [AN; patients] are eligible to receive it, but the information might take 30 days or so to trickle through different trust levels. [P-MJ]
In big centres like Glasgow and Edinburgh, implementation is usually quick, but in remote areas it could take some time. Further details related to implementation timelines are also discussed under the main theme of medicine uptake.

*It's hard for me to be more precise about implementation time in Scotland. I think that in the big centres like Glasgow and Edinburgh, they can move quite quickly as you go further. As you become more remote, I think it can be a little bit slower, but that’s where I think the influence of clinicians who have maybe been involved in clinical trials is an important factor.* [P-AK]

**The time lag between licencing and reimbursement is likely to decrease.**

Although most of the interviewed participants thought that this time lag would get shorter, some thought it would get worse. The key factors that were thought to have caused this decrease in time lag were the review of NICE methods and processes, such as technical engagement before committee meetings, earlier HTA submissions, interim access agreements or population-based agreements, the Innovative Licencing and Access Pathway (ILAP), the Early Access to Medicines Scheme (EAMS), and the UK government’s desire to lead the life science industry.

The review of NICE methods and processes is anticipated to decrease the time lag between licencing and reimbursement. For example, the technical engagement step before committee meetings would help resolve issues prior to committee meeting.

*I would hope that time will decrease as you know we learn more about data requirements there are you know that NICE methods and processes review. The whole system is trying to be quicker and better resourced because the incentive of getting product to patients earlier is huge and I would hope it would shorten.* [P-JS]

*I think NICE is working hard to reduce that timeline so the whole point is to reduce the number of committee meetings and discussions that go on between NICE and the company. So, they've implemented a technical engagement before the committee meeting, so if there*
are any arguments about the submission or the economic modelling, they want to discuss those prior to the committee meeting and make sure they're solved before they get to these discussions. [P-ALS]

The HTA submissions at NICE are moving even before the MA approval.

Certainly, we could see, this you know moving HTA submissions potentially earlier. [P-CD]

HTA submission. I think can happen even before the MA approval. [P-TH]

The Innovative Licencing and Access Pathway (ILAP) is expected to certainly expedite regulatory approval, but it will also bring efficiency to other milestones for the access of medicines. This is because all stakeholders have the opportunity to engage early.

I think it's called the ILAP which is done through the MHRA. Which is the innovative licensing and access pathway which aims again to accelerate the time to access so, so this is a mechanism for speeding that up, and I think these are what we were just discussing about when companies make those decisions about whether or not they want to engage with the MHRA on this ILAP app approach to speed up access. [P-CD]

Although ILAP can speed as there's definitely accelerated approval so this speedier timelines for regulatory. But NICE and the SMC is the same timelines. But the idea is because you've had earlier conversations that the whole process will be smoother, and you know they can fit you in at the earliest timeslot and reduce that time lag. So, I think the ILAP process will help with both England and Scotland. [P-ALS]

The government of the United Kingdom strives to be a leader in the life science business and has created various programmes, such as the Innovative Licencing and Access Pathway (ILAP), which aims to speed the time to market and facilitate patient access to medications.

UK Government want to establish themselves as the life science leader globally. I was reading the other day about ILAP application, so it looks in manufacturer for herpes vaccine was granted ILAP and the response from the NHS was like the UK is stepping to give access and generate evidence to the first vaccine for herpes because it's a global unmet need. I mean the way that you will read this is that they want to position themselves as global life science leader. [P-FT]

HTA bodies have regular conversations and do borrow ideas from each other.

I think they have regular conversations and have ideas playoff with each other you know, like SMC did some things to speed through some appraisals and I know NICE borrowed some of the ideas for that and used them. [P-MR]
Interim access agreements like the Cancer Drug Fund (CDF) and the Innovative Medicines Fund (IMF) in England, which are data collection agreements for oncology and non-oncology medicines, are helping to reduce the above-mentioned time lag. Participants provided a mixed response and were not sure if Wales, Scotland, and Northern Ireland have access to these or other funds.

I think if you want to reduce the timings between or speed up the timings for reimbursement and access, and in the context of marketing authorization. These funds are the key, I think interim access agreements are, where it needs to move towards. England and Wales have access to CDF. I’m not sure about Northern Ireland on that one actually. [P-CD]

We’ve got the Cancer Drugs Fund where if there are those uncertainties that products can go into it and they can collect more data and then go back into a reappraisal. Now we’re seeing there’s also one for the non-cancer products which is called the Innovative Medicines Fund, and that’s providing an opportunity for the non-cancer products. Maybe something like in interim access agreements that you would come with SMC and NHS Scotland. Fund isn’t there that we have in England. [P-CD]

Population-based agreement, for example, Novartis recent deal with NHS for its new statin i.e., a lipid-lowering drug to contract for 300,000 patients.

I don’t know if you’re aware of population-based agreements with NHS England, Novartis have recently signed one with a new statin injectable stadden. Now that’s, I guess, it almost runs side by side, so they got a NICE approval and then a week later. It was an agreement to with NHS, then we’re going to contract for 300,000 patients. So, the process obviously ran side by side, so I think that's encouraging because then there was a very quick. [P-PM]

Increase in time lag between licencing and reimbursement

Some participants say that the time lag could be made worse due to the high number of HTA submissions, a backlog of HTA submissions, the use of different techniques and technologies for drug development, some parts of the NICE method and process review, expedited regulatory processes, and longer negotiation times with NICE and NHS.
Complex techniques and technologies for drug development and a larger number of medicines in the development pipeline are adding more challenges to an already constrained system. High volume of HTA submissions, for example, there are 100 prospective medicines in pipeline for Alzheimer’s disease. There is already a backlog.

I think it’s set to increase to be honest and quite significantly, I think there’s a number of reasons for that. I think the first thing is that there are a lot more drug now, so you know there’s huge. The different techniques for drug discovery for drug development, so the whole sort of biologics kind of, you know, totally different ways of building medicines. There’s an awful lot more treatments, I think there’s over 100 treatments in the pipeline for Alzheimer’s disease. I mean that’s one condition, so you know the NHS isn’t gonna invest anymore in NICE, there’s no incentive for them to do that, because obviously they want to keep their costs down. And it can only take longer to get treatments through. [P-NP]

NICE is trying to make the evaluation process more efficient, which, if not done well, could slow down process.

I foresee longer gaps between licensing and reimbursement. I think the volume of assessments that NICE have to manage is large. And I know that they’re looking to change their process, which I think they are aiming to trim their process and make it more efficient. My reading of it is that it could slow them down, because if it doesn’t go well, there’ll be more challenges, there will be more appeals at the end of the process, will be more pauses or stop the clock in the middle of it to fix things that have gone wrong. So, I’m leaning towards the timelines lengthening, not shortening. [P-AK]

Expedited regulatory processes, e.g., project Orbis and national regulatory procedures are anticipated to bring regulatory approval earlier, which would be based on relatively immature data. While it is likely that regulatory approval would be granted, the data package would not be as robust as needed for HTA submissions.

Post Brexit, regulatory processes are kind of changing and perhaps becoming earlier relative to the EMA. Now with things like Project, Orbis, which is a collaboration of FDA and MHRA to accelerate regulatory timelines. So there could be some situations where you go even earlier that presents challenges for companies at the same time because often..... you could get a license based on relatively immature data, not very mature survival data, and you know you’ve met your primary end point of an intermediate, like PFS or something that could be sufficient for you to get even earlier, licensing on based on this kind of pathway. But it may not be feasible for NICE and there may be too much uncertainty in your economic model. And when you’re looking at longer term survival, which takes, maybe multiple years more data to collect, so that could drive an increase in the gap between regulatory approvals and NICE approvals. [P-FF]
Negotiation with NICE & NHS takes a long time as noted in a recent example of Vertex cystic fibrosis products.

*The vertex example on cystic fibrosis. you know they were in three-year negotiation with NICE and then NHS England. [P-DN]*

**Suggestions to reduce the time lag between licencing and reimbursement**

The people interviewed offered suggestions on how to reduce the time between licensing and reimbursement. Participants' main suggestions were to do early planning, engagement, data generation planning, and landscape analysis; have discussions with the NHS in advance about service readiness; have early communications and discussions, particularly with NICE, before committee meetings and even before submissions; to have more clarity around processes, evidence requirements, and timelines; and consider working on innovative access agreements.

Qualitative data emphasise early planning to identify available opportunities, development pathways, participation with relevant stakeholders, data generation plans, and landscape analysis.

*These types of routes (ILAP, EAMS, Project Orbis), do require a lot of very early planning.... But early engagement/early planning for those types of situations can identify the most suitable candidates and then give you the lead time to get all of the requirements in place for them. Get all the approvals you need. Get your data generation plans in place and get them all signed off and prove that all of that takes a lot of time. So that would be my first kind of major piece of advice, I would say is try to think side just try to do early planning, very early planning for your upcoming launches four to five years in advance. Map out all of those different potential routes and identify the candidates which could take advantage of these more accelerated ones [P-FF]*

*I think another would be where the majority of my kind of understanding and expertise sits at the moment, identifying gaps in in your Evidence package by reviewing your trial protocols and doing a landscape analysis on the market and really understanding the patient population of the countries that you’re going to be submitting in and then comparing that to the evidence requirements you’re likely to need based on the, NICE reference case,*
identifying gaps and then putting in place studies to or you know data collection exercises or other mechanisms to address and fill those gaps can put you in a much better position when it comes to submitting your product. [P-FF]

Early communications and discussions, particularly with NICE, before committee meetings and even before submissions could help reduce the time lag from HTA submission to HTA recommendation.

I think NICE is working hard to reduce that timeline so the whole point is to reduce the number of committee meetings and discussions that go on between NICE and the company. So, they've implemented a technical engagement before the committee meeting, so if there are any arguments about the submission or the economic modelling, they want to discuss those prior to the committee meeting and make sure they're solved before they get to these discussions with the committee meeting. [P-ALS]

More clarity around processes, evidence requirements, and timelines reduce time lag between licencing and reimbursement.

I suppose if there’s more clarity on what’s required at an earlier stage that helps. If I look at my current situation, although it is, it is a medical device. The process has changed, but it changed last week. It’s been going on for two years and then they’ve changed it. Now it’s changed in a probably favourable way because now it’s no longer feel they need to make a decision, but it’s taking them two years to decide. They don't need to decide, so I think more clarity on process and time scales will be good. on the information they need, and I think a little bit like I said a little bit more flexibility on this sort of the NHS England NICE relationship in terms of product adoption and innovation. [P-PM]

Innovative access agreements with payers could expedite the uptake of medicines.

And then at the end of that process if NHS England can produce innovative agreements to speed up adoption, then that hopefully gives everybody what they want. [P-PM]

While the HTA process is ongoing, companies need to initiate discussions with the NHS in advance about service readiness, particularly for speciality medicines that require some services to be set up for the administration of medicines.

Service Readiness is really important in making sure that, I guess while the HTA processes going on the those that are involved with from the pharma company and from there kind of NHS England or NHS trusts are kind of taken on that journey as well simultaneously so that
they know what needs to be ready so that as soon as it’s got the positive recommendation you can launch. [P-KN]

Maybe specialist centres would need to be set up. Of course, it takes time to set up these sorts of centres, but you would have discussions with NHS England in advance to try and mitigate that delay, but these are the sort of reasons why it might happen. So, it’s all about really having those discussions in advance with NHS England. [P-SDS]

5.2.2 Gap between licencing and reimbursement of medicines

Gaps between licencing and reimbursement decisions result in restricted use of treatments, which has an influence on patient access; therefore, this essential matrix was studied. Qualitative data provide useful information on this matrix, and this gap is driven by multiple factors.

The participants say that the regulators and payers think and focus on different things. HTA bodies focus on economic evidence, cost effectiveness, and budget impact, while regulators focus on clinical evidence. HTA bodies have different evidence requirements, limited budgets, and pivotal studies that are more aligned with regulators. At a global level, decision makers think about the science side, but not necessarily the reimbursement side.

This is the holy grail of questions because the way that the regulators and payers think differently, I think in the minds of payers you may have a standard of care which is very cheap. Some patients be treated ok, some patients don’t ‘t comply with the therapy. Some patients are contraindicated with the therapy. You use the therapy that is across all those populations. The cost effectiveness thresholds are very different, in one case where the comparator is doing nothing, for instance you may not want to reduce the price significantly to access this population. In another comparator where patients progress quickly and they have a very expensive standard of care, you may want to reduce the price less, so the discount offered would be less, so it’s the willingness of the manufacturer. In the absence of an international referencing pricing, I think things may be differently. [P-FT]

Licensing and reimbursement gap that’s something that would always be there. There isn’t really an initiative to make the regulatory and the HTA decisions simulates. It’s just the hope as the objectives of the two processes are just completely different. The regulatory bodies specifically, look at the clinical evidence. They look at the safety and efficacy data, so that’s it’s based on that data that they would make their decisions. HTA body bodies make their
decisions not just on the clinical data but also on the cost effectiveness data and also the budget impact. That’s the reason why the decisions are different from that of the regulatory bodies because they’re looking at a broader range of criteria to what the regulatory bodies are looking at. [P-SDS]

The gap between the licencing and reimbursement of medications is likely to increase. Some of the participants interviewed think that the gap between the licencing and reimbursement of medicines is likely to increase. The trend toward high-tech and complicated medicines, small patient populations, limited data sets, more budget cuts, the need for long-term data, poor adoption, and optimised HTA recommendations were the key things that were thought to increase the gap between licensing and reimbursement of medicines.

There is a trend for high-tech and complex medicines with limited patient populations that receive regulatory approval with limited data sets and single-arm studies. For these medicines, it is hard for companies to get through the HTA process and get reimbursements approved.

The gap between licensing and reimbursement, I think it will increase. As we go down a trend of higher technology, more complex medicines with limited data set, small patient populations and single arm studies in many cases. I think that’s harder for HTA bodies to make an appropriate assessment. So, I think there’s going to be a period of uncertainty. Which will mean that many of those technologies will not be able to positively navigate HTA process..... there will be some form of medium-term conditional approval with the commitment to go back to more formal health technology assessment once the data packages become more robust. Probably based largely on real world evidence as opposed to anything that was provided to get the license. [P-AK]

Since payers only have a limited amount of money to spend on pharmaceuticals, they would always encourage HTA bodies to limit the number of licenced patients. It is a way for NICE and NHS to keep track of how much they spend, which makes sense since they don’t have an unlimited budget.
It's the available budget that government has to reimburse the meds, so as you know every year NHS England has a certain budget for reimbursing medicines. So, by restricting the population this is saving money for the system. [P-NL]

I can speculate that with the challenges and the pressures of funding that the HTA Bodies there would be more and more pressure from the from the payers through the HTA bodies to challenge the full licenses that goes through HTA in which case you'd expect that gap to increase. [P-JS]

Restrictions are not only introduced at the HTA body level, but even after receiving a positive HTA recommendation, further restrictions are introduced by the NHS and regional/local health bodies.

Exactly you mentioned the restricted access from NICE, but that’s even and I should add, apart from NICE, you might go through the NHS process for example, you might go to regulatory or and then you go to NICE and then you get a subgroup and then from NICE. And then NHS England might restrict your population even further. [P-MJ]

There are two levels of restrictions, not just one. And that’s after regulator and NICE. And after NICE is NHS England. So, at every point pharma companies need to be very sharp to ensure that access is not overly restricted. [P-MJ]

Although companies are getting regulatory approval based on limited data set which is not robust enough for HTA bodies, this becomes even more challenging with the requirement of long-term data by HTA bodies. Eventually, there are more restricted recommendations.

I think gap between licensing and HTA decisions is increasing over time and a lot of that is down to the need/requirements from HTA bodies to have longer term data. They are taking, that lifetime horizon and I think the rigor of NICE requires additional data a lot of the time and particularly in the last few years, we’ve seen that like even increase that. Companies are receiving a marketing authorization on a trial and that may not suffice from HTA perspective and that’s the reason why we’re seeing more subgrouping or negative recommendations being issued. Because there is that discrepancy between the needs of the regulator and the needs of the HTA. I know there was one academic health economist who said that the regulators are abdicating their responsibility onto the HTA authorities. [P-CD]

Drug development decisions are made at the global level thinking about the science side, but not necessarily the reimbursement side. Pivotal studies are more aligned with regulatory requirements.
When global decisions are being made globally about how to develop treatment. They’re obviously thinking about the science side, but not necessarily thinking about the reimbursement side. It’s kind of a long-standing kind of issue. [P-NP]

The product I’m working on it’s used for patients who have chronic kidney disease. When the study started... some patients were on dialysis and some patients weren’t. They found a really good outcome in one group, and a fairly ordinary outcome in another group. You ...get a license across both groups. But when you come into cost effectiveness because one group gets a much better outcome than the other, one looks much more cost effective. Then NICE is going to say, we’ll fund that group where it’s cost effective. But we won’t fund it in the other group, and it’s quite a difficult problem to solve that. The key thing is to get your research right. But unfortunately, until you do the study, you won’t necessarily know who’s going to benefit and you don’t want to then go back and invest in more studies to try and plug your gaps. [P-NP]

The gap between the licencing and reimbursement of medicines is likely to decrease.

Some respondents are of the opinion that the gap between licencing and reimbursement of medications is likely to decrease. Focus on more specific and targeted therapies, interim funding in England, Wales and Northern Ireland (CDF and IMF), and new processes such as ILAP, review of NICE methods (change in end-of-life criteria to severity criteria) were thought to help close the gap between the approval of medicines and reimbursement of medicines.

As more specific and more targeted therapies are being developed, there is an expectation that the gap between licencing and reimbursement of medicines is likely to decrease.

But on the other side would we have trials that have become more specific and more targeted in which case, you might expect the HTA recommendation to match the regulatory license which would reduce that gap. [P-JS]

The introduction of interim funding arrangements (e.g; CDF & IMF) initially for oncology medicines and recently for non-oncology medicines is thought to reduce the gap between licencing and reimbursement of medicines.

Like I suggested earlier, kind of having that interim initial funding system could help improve access and I think better service. [P-KN]
A new UK initiative, Innovative Licensing and Access Pathway (ILAP), is expected to bridge the gap between medicine licensing and reimbursement. While it is likely that this initiative will reduce the gap between licensing and reimbursement in the UK region, it could bring more variability between the UK and EMA region.

I guess new initiatives like ILAP might help from UK GB perspective. But we could if you go down the ILAP app it could lead to being divergent from the EMA, perhaps and kind of having inequality vs Europe and Ireland as well, which is obviously part of the EMA. So, it might be positive in terms of having a license and reimbursement and it's more kind of GB focused and that it might make take us further away from our neighbours. [P-KN]

NICE methods review (e.g; change in end-of-life criteria to severity criteria) could possibly reduce the gap between licencing and reimbursement of medicines.

There are few things that was brought up in the NICE methods review. So before at NICE drugs that treated conditions at the end of life were considered to have a higher threshold and the NHS will pay more for those. So, they're proposing changing that to severe diseases, so not just ones that treat end of life, so if you've got a chronic lifelong condition that proposing changing the end-of-Life modifier to a severity modifier, so that will hopefully help access for people with lifelong conditions. [P-ALS]

**Suggestion to decrease the gap between drug licensing and reimbursement**

The participants who were interviewed offered suggestions on how to shorten the gap between the licencing and reimbursement of medicines. Participants’ main suggestions were to allow access through interim arrangements and then do a more formal HTA, to look into and deal with problems with how medicines are used at the regional/local level, to allow access at the point of licence and put restrictions on it later, like they do in Germany, and to get involved early.

Access is primarily obtained through interim arrangements, which are followed by a more formal HTA process. This would not only avoid a negative recommendation but will allow
access to medicines while company is collecting additional data for the full recommendation later.

I think if you want to reduce the timings between or speed up the timings for reimbursement and access, and in the context of marketing authorization. These funds are the key, I think interim access agreements are, I think, where it needs to move towards and what that means for companies is that you need to go away and collect further information. In some ways you’re delaying the formal recommendation until later, but you’re having interim access and it allows for patients to have the medicines. [P-CD]

I think then there’ll be some form of again medium-term conditional approval with the commitment to go back to do a formal, more formal health technology assessment once the data packages became more robust, probably based largely on real world evidence as opposed to anything that was provided to get the license. [P-AK]

Companies should have opportunities for access at the time of licence like in Germany, while more formal HTA evaluation and recommendation can be completed later. Companies must explore and address challenges of medicine uptake at local level.

To reduce the restrictions at local level, I think maybe kind of education on the with the kind of local levels on the on the drugs and maybe working with those that come up with the treatment algorithms to kind of develop which ones are kind of more suitable and maybe trying to help roll them out in a more standardized fashion across the local levels. [P-KN]

Let’s say the process that the UK has is the best to allow early access to innovative medicines, so I guess if you compare the UK system to the German system, for example, which allows kind of access at the point of license, that then puts restrictions kind of later on. Whether an approach like that would allow kind of early access to medicines in the UK and allow you to collect kind of real-world data on kind of what the medicine is actually like in clinical practice before making the decision on whether or not it should be based on the cost effectiveness. [p-KN]

While it is typical for HTA bodies to possibly restrict licenced patient population if required, companies should try to engage with HTA bodies very early in the development process, e.g., at the stage of planning the trial.

I think that’s difficult call because there’s a tendency yet at NICE to micro slice populations .... NICE actually want you to do an analysis in this population that you’ve never had a plan to do an analysis and you end up with a complicated situation. The only way to really reduce it effectively is to have more early dialogue between HTA bodies and pharmaceutical companies to be more aligned on what are the important things to measure and the
important populations to assess? When planning your trials, they’re going to be a regulatory trial. And I, I think that that is something that is improving overtime. Both NICE and pharmaceutical companies are getting better at working with each other. I don’t know what it’s like for the SMC side, because I have not been inside of that. [P-MR]

5.2.3 Differences/Variability in HTA recommendation / reimbursement between countries in the UK

Qualitative data demonstrate the variation in HTA recommendations and reimbursements between UK countries. Additionally, it explains why HTA recommendations and reimbursements vary, discusses the trends in the variability of HTA recommendations and reimbursements among countries, and provides ideas for reducing the variability.

According to participants, strategic priorities and political considerations are the main reasons why HTA recommendations and reimbursements vary from country to country in the UK. Many countries use the NICE decision as a point of reference, and there are independent HTA bodies. Epidemiological differences, the results of HTA are not always the same, or the results of HTA are hard to predict. The HTA evaluation time for NICE is longer than for SMC. Differences in how an evaluation is performed and how it is performed, ICER threshold, interim funding arrangements in England (CDF and IMF). SMC not having a way of dealing with additional data collection, resubmitting an HTA is easier in Scotland but hard in England. NICE is tougher to get through than SMC; in the past, it was harder to get through SMC than it was to get through NICE. The capacities, budgets, and resources of HTA bodies and pharmaceutical companies are different.

The process of obtaining patient and clinician variability is higher for treatments for rare diseases due to the number of people involved, the infrastructure required to make it
happen, differences between NICE committees and evidence review groups, and differences between the different NICE committees and evidence review groups.

SMC focused more on the cost of the drug, while NICE looked at how it affected quality of life. NICE decisions are thought to be stricter than SMC decisions. Variability has both pros and cons, such as differences in how it is used at the local level and in the standard of care that is already in place.

The differences in strategic priorities, political considerations, regional needs, devolved health systems, and legal requirements to meet the local health needs are considered the key reasons why HTA recommendations and reimbursements vary across countries and regions in the UK.

*I guess the other one relates to probably as strategic priority e.g., in England you know mental health is kind of where lots of spending is being directed, but maybe in Scotland there is something else.* [P-FT]

*Remember that all of the commissioning initiatives so all the reimbursement responsibility in England, Scotland, Wales, Northern Ireland is local. System was designed that way, so if you look back at the history of sort of policy direction, guidance, statutory instruments to local commissioning groups, clinical commissioning groups before that, PCTs before that health authorities, they were mandated in law to take account of local health needs and Commission services it to meet those local health needs. So, postcode prescribing was not an unfortunate consequence. It was a duty. It was a legal requirement. ....... It's how the system was designed.* [P-TJ]

The difference in the existing standard of care in individual countries/regions could also lead to variability in the HTA recommendations/reimbursement.

*How do you ensure that it (AN: new treatments) fits (AN: have same status of access) all the countries, considering that all the treatments that already exist are different.*
Since NICE and SMC are completely separate HTA bodies, Wales also has an independent HTA body, but Wales and Northern Ireland typically adhere to NICE's decisions. As independent HTA bodies, these organisations have different responsibilities, objectives, evaluation processes, and decision-making processes. This also results in in variability in adopting HTA recommendations.

So, the HT application process is slightly devolved in the sense that England follows its own rules. Scotland has a slightly more independent approach to access decisions or the HTA decisions. Northern Ireland and Wales, though in theory they are independent, they tend to follow NICE, which is England’s HTA body quite closely. I mean, they do have their independent bodies, but they tend to follow the NICE recommendations much more closely than Scotland. [P-SK]

I still see them acting individually, I haven’t noticed that I see initiatives like we had spoken about in England to speed up the process and speed up adoption and so on. But it that’s still, that’s England you know you could go to Scotland and it’s different or they could have the same initiatives, but they would be implemented in a different way. So, I still don’t see any huge desire to reduce variability. Personally, I haven’t seen that. [P-PM]

The variation in HTA recommendation and reimbursement is also the result of inconsistency and lack of predictability of HTA results. There is a lot of inconsistency in NICE decisions compared to SMC. Although some participants were of the view that overall recommendations are not that different as there is minor variability, others acknowledged the presence of variability but also noticed a decrease in the variability.

I would say and there's still a lot of inconsistency about how companies are using that (AN: evidence packages) and how even NICE and HTA bodies are kind of accepting some of those evidence as well. I think SMC take more pragmatic approaches in their reviews and there is a lot of inconsistency in NICE. So obviously you know that there are different evidence review groups and each evidence review group has their own kind of individual style. So, you’ll kind of find out the same for the committees as well. [P-KN]

In terms of consistency of decisions across HTA bodies I think majority of my peers would say that working with the SMC is more relaxed. There is more to and from, whereas working with NICE it's a lot more you versus them. And even within the committees, they operate very differently. The chairs are different. And the ERGs, are very different. [P-SH]
They’re usually pretty similar on the overall recommendation. There’s been some previous studies into that. Also, most of the variation is pretty minor in terms of the overall decision. I think we’ve seen a reduction in that variability over the last, you know, decade already know what the threshold is, you know, beyond which you can’t reduce the variability. I don’t know, so I’m hopeful that variability can be reduced. [P-MR]

Although SMC used to follow NICE historically, it appears that SMC is now recommending more therapies and even at a good pace for certain medicines compared to NICE. It also appears that this variability is decreasing.

I have seen in the past that SMC usually follows NICE. Increasingly we see SMC recommending more therapies and in sometimes you know, in certain therapies faster. I think it’s probably something we observe is like this gap is narrowing down between England and Scotland, Wales follows England anyway. [P-FT]

Another variability is the speed with which the evaluations are performed. The HTA evaluation time is considered relatively longer for NICE compared with SMC.

One reason that I may think of is that SMC is slightly faster. I would say in terms of their decision and then so if the company would like to have a reference from UK HTA body faster so they can go through SMC. [P-NL]

I have seen differences in the past across countries. I’m not familiar enough with the detail of the process. I think one of key difference in the past has been the speed with which the reviews have been conducted, and it’s I believe it tend to be faster in Scotland. [P-JS]

Differences in evaluation processes and methodology are another source of variation in HTA recommendations and reimbursement. For example, some medicines would not be considered cost-effective due to the criteria and framework used by NICE, when compared to SMC. NICE has better capabilities to deal with high-technology economic modelling compared to SMC. Sometimes variability is the result of differences in opinions among key consultants involved in the process.

I think that NICE has a higher capability of dealing with very technical health economic modelling, the SMC don’t have the resources to deliver that type of expertise, so if you do some really funky health economics, NICE might get it and say they understand that, and we get it. However, SMC might say that’s just too complicated. Give me something simpler please. [P-AK]
Whilst you know the principles of economic evaluation and health technology assessment are broadly comparable there are some differences within terms of the methods used, and the process used. For example, in cancer where you have a medicine that would qualify for some of modifiers for SMC because of the broader nature of them, which would allow you to demonstrate cost effectiveness. But in NICE, you wouldn’t have the same mechanisms in place and then for the same medicine wouldn’t be considered cost effective by the framework and criteria that NICE have. [P-FF]

While NICE has clearly defined and more stringent thresholds for the incremental cost-effectiveness ratio (ICER), SMC and AWMSG do not have published thresholds and are relatively flexible.

It’s often down to different methods and different treatments. So NICE has definite thresholds for its cost effectiveness. So, between 20K and 30K standard drugs, 50K for end of life and 100K for rare drugs. Whereas the SMC and HTA body in Wales they don’t have published thresholds. [P-ALS]

Compared to NICE, SMC in Scotland has a better ability to review and recommend treatments for rare orphan diseases. These differences lead to variability unless criteria are aligned due to ongoing changes in NICE methods and processes to evaluate medicines.

For Scotland because it already has a better ability to use disease modifiers. And when it comes to looking at things like rare diseases and those types of things that at the moment doesn’t exist with NICE, but it might do once the new methods manual is published, because it’s one of the important factors that they’re looking at to reduce or get or move away from the end-of-life criteria which was specifically for oncology to a severity modifier that could be applied to any disease that meets these certain criteria. So that’s one thing that I think is different but may soon equalize. [P-AK]

SMC places more emphasis on the cost of the drug, while NICE considers the impact on quality of life.

SMC put a lot of emphasis on the cost of the drug if you accommodate the cost then Scotland is more willing to give a positive recommendation. Sometimes the two of them connect each other so they know their influence. However, in NICE they took into account the impact on quality of life. It’s a much more comprehensive process. [P-VS]

NICE decisions are considered more restrictive than SMC.
I think it depends very much the product then the disease area. Usually, the vast majority there will be alignment between the indications and the recommendation. Ideally, that would be within the indication that the marketing authorisation is in, but you do find subgrouping or restrictions across the organisations. I know just from my experience or from seeing different recommendations coming out of NICE and from SMC, I take it may be fair to say that you see more subgrouping or restrictions put in place by NICE compared to SMC. [P-VS]

Differences in interim funding arrangements in different countries and regions also contribute to variability in HTA recommendations and reimbursements.

We’re seeing an expansion of a mechanism in intermediate in interim funding, which you may have heard of called the Cancer Drugs Fund, which is now being expanded to the Innovative Medicines Fund and it’s going to include more disease area disease types rather than just cancer. P-FF]

Wales do indeed get any share from these cancer drug funds because of that remit and it’s funny. It’s all down to timing when it comes to Wales, I think you know, sometimes companies do go down the route of the AWMSG approval because they may not have the NICE approval or have submitted to NICE for varying reasons. But because of that, you do find that yes, that Welsh patients will have access to the medicines if it’s on the Cancer Drugs Fund. And same applies to Northern Ireland as well but NI also sometimes can decide to take its recommendations from Scott. So Northern Ireland, do things slightly differently. Maybe something like in interim access agreements that you would come with SMC and NHS Scotland. presently Fund isn’t there that we have in England. [P-CD]

Although in England there is a way to deal with additional data collection, SMC is not equipped to deal with this requirement if applicable.

I think for example, its data driven uncertainty, I know that SMC doesn’t have a way of dealing with additional data collection, whereas NICE does, so potentially they could start sharing data that is collected for NICE to eliminate such restrictions. So, if it’s data driven then SMC can do something about it and actually now within new licensing processes that will contribute ILAP that will be able to participate in meetings so they could address part of that issue. If it’s not data driven and it’s cost effectiveness driven, then obviously it’s not the HTA agency fault, it’s the manufacturer that needs to come to a different understanding. [P-DN]

Resubmissions of HTA are considered easier and quicker to file in Scotland but more difficult in England.

The difference, again, I would say there is that even if Scotland had decided no, and you can resubmit your data next month or the month after…… In England it’s much more difficult to do that. It’s a much longer time delay. If you then go back in with what they still call it a rapid review. There’s nothing rapid about it. To be fair, it’s pretty slow. [P-JS]
Differences in resources, budgets, capacity, and infrastructure for implementation between HTA bodies and regional and local health organisations also contribute to variability.

I think it’s bit political, it has to do with the budget as I told you how they allocate their budgets, and it doesn’t have to do purely with these medicines. It has to do with the budget in the whole healthcare. So, the population also sometimes we have differences in the epidemiology. NICE impact, a lot of other markets globally, so it’s the Golden standard. SMC seems to lack resources for the staff, etc to implement the more sophisticated method. You will always have differences because also the committee is different, the doctors, the trends. I don’t know if it would be the benefit to have one national decision for medicines. May be epidemiology justifies some decisions in Scotland and not in England. [P-VS]

I would say one thing is the capacity of the HTA bodies. NICE is much more well equipped with people and research scientists and the other hand; SMC don’t think it’s so good to assess all those submissions in in depth. [P-NL]

Differences in resources and capacity between pharmaceutical companies also contribute to variability. For example, some companies have more experience in one therapeutic area than in another. Some companies are equipped enough for submission to SMC but not for submission to NICE.

Companies need to hire smart people who understand these differences. I’m not sure it’s the responsibility of NICE or SMC. I think its responsibility of companies to understand that there are different organizations with that have a different way of making judgments and assessments. Understanding their variability, understanding the history of other products that have gone through one of the four NICE committees or the very one SMC committee because, and again that can determine how you make an approach. You look back at history, you look at some of the things that have happened and have been documented. There’s much more documentation with NICE than there is with SMC. So again, it’s I think it’s up to companies to understand how to navigate both systems. [P-AK]

Differences in various NICE committees and evidence review groups could also contribute to variability. Variability tends to exist more in rare disease treatments.

I think sometimes also there is variability in access because of the fact that maybe especially for rare diseases. There are some cases where, for example, there are only 50 patients in England and if you look at SMC compared to the population of England, maybe there are only two patients every year, so every two years in Scotland. If you think about the costs of a submission and if you think about submission for just two patients in in Scotland. Seems like quite a lot of work versus the potential that you’d get for patients were using it and Outside of that patient still have access to drugs through a system called the individual patient.
request system in Scotland. So, it might be those 2 patients would receive the drug anyway, irrespective of whether you actually have access or not. [P-MJ]

The variation in HTA recommendations has its pros and cons. For example, if NICE has said no and SMC has said yes, it is a pro, as if NICE’s no was applicable for all of the UK, no patients would get reimbursement, but due to the yes from SMC, reimbursement of treatment would be available at least for patients in Scotland.

Sometimes you might end up with an SMC yes and you get a NICE no. So patients in Scotland might get access, and patients in England don’t have access. I think that in itself is a pro and a con, pro in the sense that you know there are independent processes, which means that if NICE says no then at least patients in Scotland might have access. Whereas if they streamline and make it all into one process, if NICE says no, it will automatically be no for all over the country and a lot more patients are missing out. I just don’t know if working together also equates to the same decision. It might be that share the information but in the way they interpret the information might just be different because they might have different standards and different costs and different cost controls to medicines. [P-MJ]

Variability is not the result of HTA restrictions alone; it also involves differences in adoption at the regional and local level, particularly in England.

Having devolved health systems throughout the UK naturally leads to inequality. But even once HTA decision is made, the provision of service locally is so different in England. I think inequality is huge agenda item for the NHS. [P-PM]

And there's also the possibility that you have a NICE recommendation that's not restricted. But then in practice, it's prescribed in a restricted manner. [P-MR]

Decrease in Variability

Some interview participants anticipate that variability is likely to decrease. This likely decrease in variability is thought to be driven by the UK government's priority to fund health services in all areas: the Innovative Liencing and Access Pathway (ILAP), the NICE methods review, standardised formularies, standardised guidelines, and treatment policies; and HTA bodies talking more with each other.
The Innovative Licencing and Access Pathway (ILAP) is a new initiative to facilitate access to medicines, and it offers an opportunity to agree on a few aspects of evaluations. For example, there could be agreement on scientific evidence and product core profile, but there would still be differences in the cost-effectiveness analysis. There could also be differences in the data when comparing the local population.

I think we’ll have to wait and see how it plays out...... ILAP is a consortium of clinically and scientifically oriented people. There is opportunity when you have because the signs of the disease don’t change and data interpretation, the grass level data interpretation doesn’t change much. What changes is the safety efficacy parameters and pharmacodynamics parameter of that particular product. And how does it compare in your local population that changes. so, when NICE is working on its own, it’s looking at English population, but working in ILAP I think there would there likely to more agree on the science and the products core profile itself. Where they would differ is for example the cost effectiveness analysis...... So, I don’t think that second gap would ever close. It can speed up the process. [P-SK]

The UK government has given priority to funding health services in all regions and introduced various initiatives, eg the ILAP application to facilitate access to medicines, the quick introduction of the Covid-19 vaccine, and a vaccine for herpes, which is in fact a global unmet need.

I mean the UK Government want to establish themselves as the life science leader globally you have already picked up the news with COVID and the vaccines and etc. I was reading the other day about ILAP application, so it looks in manufacturer for herpes vaccine was granted ILAP and the response from the NHS was like the UK is stepping to give access and generate evidence to the first vaccine for herpes because it’s a global unmet need. The ILAP also has NICE and SMC and MHRA together. This tells me that the variability would be probably reduced, and I think the kind of therapies that you see in England you will see in Scotland. [P-TH]

The NICE methods review, and anticipated changes may aid in closing the inequality gap between England and Scotland. These changes are expected to reduce variability.

So one interesting development that’s happening at the moment is NICE doing a review of their methods and processes. So that’s been in consultation for the last couple of years but they’re getting to like towards the final stages of determining what changes they’re going to make. I very much doubt there’s going to be any changes to the threshold. But we could see further flexibility around modifiers in certain situations, which I think is one of the key issues
Smaller regional and local organizations, such as Primary Care Trusts (PCTs) and Clinical Commissioning Groups (CCGs), are being replaced by relatively larger bodies, such as integrated care systems (ICS), as a result of recent changes in the health care system. These modifications include the expected emergence of more standard formularies, guidelines, and treatment policies, which would reduce variability.

Now we’re moving to integrated care systems that local population requirement is still going to be there in law, but the populations we’ve got bigger. We used to have 230 PCTs and we will now have 44 ICS so the variation must diminish because there will be standardized formulary, standardize Guidelines, treatment policies. Low clinical value policies across 1 to 2 million people whereas in the past they were across about 300,000, so that must reduce the variation. I think with ICS there will be they will have lots of flexibility about delivery. So, I think the distance between the local healthcare provision and the Secretary of State is going to get shorter with these larger organisations, so those are the plus. I think the journey to a national formulary feels inevitable to me and that sort of overlays that. I think that’s what’s happening in England [P-TJ]

I think in Wales, I don’t think you get so much variation anyway, and the same in Scotland because health system is devolved function, those governments are taking an active interest. In making sure that every area has the same range of services and the same approach to expensive treatments and so on. So, I think all of those things are reducing the degree of variation. [P-TJ]

Although HTA recommendations and reimbursement vary between countries in the UK, it is predicted to decrease. This decrease in variability is a result of HTA bodies collaborating more and being more willing to learn from each other’s experiences.

I think definitely less variability in future for sure. That’s because I feel SMC and NICE are collaborating a lot more. I believe now with Brexit, and their reliance on MHRA, NICE and SMC are definitely collaborating lot more. I’ve been involved in joint calls with both SMC and NICE to discuss specific applications. SMC is always quite keen to ensure that you know patients in Scotland aren’t too far behind in gaining access to patient compared to patients in England. I would say in terms of where we’re headed is certainly less because SMC and NICE are collaborating. There was a recent press release that Wales is now also opted into and the part of this partnership. I presume rather than two way there will now be three-way
discussions with Wales, SMC as well as NICE to ensure that those other nations are not missing out on access for patients. [P-MJ]

It seems that the last couple of years HTA Bodies are communicating more with each other and they’re communicating more in terms of the price. Also, I know that there are people from SMC observing and be part of NICE processes. So, when the product comes to SMC, they are already aware of it they have this background of information, so it’s easier for them to expedite things and make their recommendation also. So I would say with the current, facts, I think the viability will decrease in the future. But you are right then we have seen different recommendation and restrictions amongst the two HTA bodies. [P-NL]

Increase in variability

Some interview participants anticipate that, due to the factors below, variability is likely to increase. Participants think that the NICE Methods Review is to blame for this likely increase in variability. This could lead to more restrictive recommendations, inconsistent NICE HTA results due to different ERGs and committees, shorter submissions in Scotland, and patients having a strong say in the HTA process.

The review of NICE methods can result in more restrictive recommendations. While the SMC processes do not going through any major changes, they will continue to act as before and continue making recommendations to a larger population compared to NICE. Consequently, due to the increase in the gap between NICE and SMC decisions, variability is likely to increase.

I think variability will increase. Currently there’s NICE methods review on going, where NICE are going through a public consultation of all of the methodologies for their reference case and the process. I do think that you know the likelihood is that we will see further restrictions and subgrouping of populations from NICE. SMC because they aren't going through this process. They seem to be sticking with what they have currently. I guess given that SMC seemed to recommend broader compared to NICE. It’s likely that we’ll see a further divide. [P-CD]
There is inconsistency in the results of the NICE HTA due to different ERGs and committees.

If NICE continues to outsource work to external bodies, it would continue to impact the recommendations and could lead to more variability.

We have seen in the past NICE outsourcing stuff to external companies. They didn't have the knowledge and understanding and the awareness of the disease area, so their comments were not really making sense. If I can put it this way because they didn't have this NICE mindset and understanding. So, it really impacts the outcomes. [P-NL]

Variability is likely to increase as long as HTA bodies continue to follow the same approach and practices. For example, patients have a louder voice in the SMC process than in the NICE process. Additionally, depending on differences in comparators, standards of care, or even in licenced populations, it would be challenging to contain the variability.

I would probably anticipate variability to grow. If you've already started with different levels of access in each country. If you've got more competitors coming in, they're going to be facing different challenges in each country, if that makes sense, so you might have different comparators or they might have been licensed in different subgroups, and that's only get worse overtime not better. [P-KN]

I think with Scotland being more pragmatic, it may be leads to kind of recommendations that are broader. Sometimes they're more restrictive, so it's hard to kind of call it either way. But I guess they promote much more of a kind of cost minimization route or abbreviated submission route. So, if you have a medicine that's within the same class of some things already, they kind of accept that type of HTA appraisal, whereas NICE is very sceptical of doing that kind of approach, so that will always lead to differences as well. [P-KN]

Patient advocacy groups sometimes are forgotten, but they have a lot of say. They have a big voice, but I think in the SMC their voice is a little bit bigger than in the NICE process. [P-SH]

Suggestions to decrease the variability

Participants in the interviews suggested ways to reduce the variation in HTA recommendation and reimbursement in UK countries. Participants made suggestions like having HTA bodies work together more, getting involved early, using Real-World evidence (RWE) data, making prices more flexible for both regions, putting HTA submissions
in a well-planned order, and having HTA bodies that are independent but use the same evaluation process.

More collaboration among HTA bodies is key to addressing the variability in HTA recommendations. HTA bodies need to collaborate more, talk more, and be more willing to learn from each other's experiences.

I think if there was better communication between the countries, the regions, this would very much be different I think and a greater understanding of the inequality of health within their region like so. For example, if we knew that more patients in Scotland were affected by particular disease. Then you would see and be able to understand the variability, but if the patient population, the number of patients were pretty much the same with between England and Scotland, you wouldn’t expect to see such a variability. [P-SH]

An increase in the use of real-world evidence (RWE) data for the assessment of HTA could help reduce the variability.

I guess to reduce the current variability it would be a hard task to kind of look at the real-world evidence that you have from both nations. In Scotland, maybe you’ve reimbursement for the full population, whereas in England you’ve reimbursement as subgroup. Does the real-world evidence shows that it is actually cost effective in the full population or the subgroup and kind of tailor their responses based on that and obviously NICE do the Cancer Drugs Fund and they might do kind of re reviews, but obviously Scotland doesn’t have that option so they’ve gone for recommendation straight away. And so maybe Scotland could look at when NICE does look at CDF review and think oK should we align based on the fact that we’ve got kind of two years of real-world evidence to show what the drug is like in the UK. [P-KN]

If pharmaceutical companies were more flexible with pricing in both regions, it would be helpful to reduce variability.

In terms of advice on how to reduce the difference, companies are constantly needing to balance the desire to fulfil patient needs. With the tension created from a commercial viability point of view and so pricing obviously becomes a pivotal kind of component in that equation. If companies are able and willing to be more flexible on price for England, in a way that they’re not for Scotland then sometimes that can reduce the gap, but very often you’ll see that inequality because companies aren’t willing to offer different prices between the two nations because they view it as unfair. Very often you’ll hear kind of payers in SMC trying to inquire and attempting to find out what net prices are in England because they suspect strongly that England are paying less and very often that can be the case. But legally that’s, you know, a confidential net price. [P-FF]
Pharmaceutical companies that have flexibility around the sequencing of HTA submissions could also help reduce inequality.

The other thing I would say maybe to reduce that gap is to think about the sequencing of your submissions. Very often you could be in situations where you are engaging with a NICE process, and you’ve planned to do SMC. If your timeline starts to get delayed for either strategic reasons or for like issues with the regulatory process or issues with like data readouts and all the whole host of things that can happen and result in delays to NICE submission. For companies to still have the same commitment to SMC that they originally intended. So, it would be helpful for companies not to allow strategic decisions made for NICE to not have a knock-on effect to SMC submissions. [P-FF]

But sometimes companies can say ok, well if we’re delaying NICE, then we’re delaying SMC as well, just from an internal resourcing perspective. So, it’s not always possible, but I think. It’s one area that could end up in reduced inequality, let’s say between the two because one impacts the other. [P-FF]

Having independent HTA bodies is good, but uniformity in the evaluation process could help reduce variability.

SMC have a very different sort of criteria. For example, they have PACE. They listen to the patient voice and clinician and it’s more than England. For England it’s all about cost, effectiveness. Again, they listen to that as well but it’s kind of evolving. So I think it might bring equality from the system point of view that everybody will be evaluated the same way. But for pharmaceutical company you will find some drugs will not be submitted because of the limitations within the data because of for example the criteria being set by the pan UK bodies, which I foresee as a more restricted one then we currently have. And at the end of the day, maybe all of the patients in all the four Nations would not get access to some of the medication in the end. [P-SR]

So, if you need to have a balance really to be honest. What I think would be useful is to have a uniform process across. I don’t think so that having one would be beneficial. Having four is fine, but as long as there is a same criterion, there is a uniformity in decision making. There is a uniformity in the clinical opinion that this is the right outcome measure. [P-SR]

5.2.4 Impact of Brexit on access to medicines

In response to a Brexit-related question, interviewees highlighted the following factors that would impact the UK’s access to medicines situation.
According to participants, the shift in regulatory responsibilities from European Medicines Agency (EMA) to Medicines and Healthcare Products Regulatory Agency (MHRA), the sequence of licencing application filing, the impact of resources, and the MHRA’s new working model (collaboration with other regulators, e.g., Reliance, Project Orbis), early and closer collaboration between regulatory, HTA bodies, and payers, the drive to bring medicines to the UK earlier, and the challenges of the parallel trading market were the key factors considered to impact the access to medicines situation in the UK.

Following Brexit, there are risks and opportunities with regard to access to medicines in the UK. The impact on the sequence of licencing application filing is a major risk, as UK licence applications may be deprioritised or delayed.

*I think it’s a greater risk because of the challenges we have with reimbursement in the UK, which most companies recognize that the UK regulatory submissions could be deprioritized behind the EMA. So, we may end up being something similar to Switzerland.* [P-AK]

*It’s certainly a risk. I guess it’ll be commercial decisions to be taken by each of the manufacturers. But if you’re looking at a product where actually the prevalence is the same across the whole population in Europe then if you got to prioritize this submission. You’d prioritize your EMA submission over your MHRA submission, because it will just cover more people and you can move onto the reimbursement in those markets more quickly, and so certainly if it comes down to patient numbers in a disease area like that. I would say it’s certainly a risk. I don’t know enough about the differences between the EMA and MHRA submissions, what’s sort of synergies there are in regulatory submissions, but if they’re quite different and you’re not investing in a UK specific team, it will be a risk.* [P-JS]

Considering the fact that the UK is being used as a reference country for pricing, it is more likely that submissions from the UK will not be prioritised.

*I think there are about 60 plus countries that refer to UK in terms of their price point. It has a very important role in the World Health care system because of that. It automatically influences your price in other markets. But because the price in UK tends to be high from the pharma companies’ point of view, I can achieve a higher price in most other markets as well. So, because of that, I don’t think there can be prediction to deprioritize UK.* [P-SK]
UK licence applications, which were previously covered through the submission of EMA, have an additional burden for pharmaceutical companies as well as the regulatory body. There is human resource impact at all stakeholder levels, particularly due to the shift in regulatory responsibilities from EMA to MHRA, as companies have to file an additional licence application with MHRA.

So now they (AN: Pharma companies) have to have extra people working on the UK (AN: Regulatory submissions) So, it depends on the company. If you are Pfizer or Astra Zeneca, I guess it doesn’t matter. You have resources so you would file at the same time, or you even file the UK first. Well (AN: from regulatory body perspective), it depends on the workload of the MHRA. For example, now if they want to, they need to have enough capacity to review the product. The nice thing about that is that they are actually being the only regulatory body, it’s normally supposed to be quicker. [P-TH]

But again, the Brexit thing could have an impact from human resourcing perspective, I think. Because as we have seen, not the frequency and the amount of people that come into work is low. [P-NL]

We also anticipate risks related to the supply of medicines due to Brexit.

I think that would all depend on the company prioritizing the UK for supply. Before it the UK was aligned with the EMA. Although they always have a separate process for NICE, they’ve got this additional burden of the UK MHRA license now, so that’s an extra step that companies have to go through. So, the actual patient coverage in the UK there’s a potential for it to be delayed because of the problems with the additional steps that companies have to go through now because of Brexit and also supply issues..... Although I’d like to think the ILAP process things would speed up, I think with the problems with drug supply and getting drugs for the patients, I think there would probably be a delay. [P-ALS]

Some participants were of the view that there is an opportunity for the UK to become a leader in life sciences if they can address the challenges and bring about efficiencies not only at the regulatory level but also at all stakeholder levels.

There’s a big opportunity here I don’t feel confident in saying that at the moment. But I do think it’s system wide, so it is not going to be MHRA and NICE alone. The life sciences part of government needs to be aware of this, that if they want to sell United Kingdom as a place to continue to be an international leader in science, then they will have to step in and help fix this problem because there’s no point doing clinical trials here. There’s no much point doing...
R&D here. If you can rapidly get through regulatory but then actually nothing else happens, that’s an embarrassment for UK. [P-AK]

So, it’s saying in terms of timing, there is opportunity to improve it with MHRA being able to work so much more closely with NICE and NHS England. So, there could be some good opportunity there and we are seeing reference to them working together. I don’t know yet know how exactly that will work, but there are positive noises around that and in terms of the coverage and the label. [P-JS]

I’ll give you an example, it’s definitely not lagging, in fact. I have to admit, it’s had the opposite effect. We are launching in UK, thinking of launching in UK in many instances even before launching in other countries. [P-SK]

It appears that MHRA might explore different models and pathways for licencing medicines when compared with the EMA, which could bring more divergence in the region.

I’d say I see both risks and opportunities. The impacts of those changes and there could be increasing divergence overtime potentially I guess because of how recently Brexit, occurred and how intrinsically linked MHRA was historically to EMA. You still see a very broad alignment between the processes but overtime those could start to deviate because the MHRA have their own mandate now. For example, things like Project Orbis, where we’re kind of collaborating more with the FDA. So, some companies may see that as an opportunity if they can make efficiencies with their regulatory processes. Already pharma companies go to FDA earlier than the EMA, broadly speaking anyway. So, I think that could be an opportunity for MHRA to kind of piggyback off that in a lot of cases, if not all cases and obtain earlier licensing as a result of that. [P-FF]

It was also observed that the MHRA is considering being flexible in its approach but if NICE is not showing the similar drive, there could be an increase in the gap between licencing and reimbursement.

Government wants to sell the UK as a place that can do really rapid turnarounds for innovative medicines. So, the ILAP path through MHRA is fabulous. My regulatory colleagues tell me you couldn’t design a better regulatory pathway if you try it is ideal. However, you still going to bump up against the NICE process. You might argue an early marketing authorization with a data package which is even less robust. How can you possibly then get a positive recommendation out of NICE. So, at the moment I’d say those two things are misaligned. Ambition of the MHRA with its rapid review process doesn't fit with the needs and requirements of a very firm, robust, highly technical methodology for HTA so that I think is the greater risk. If MHRA is starting to become more flexible, but NICE isn’t, I think the gap widens between licensing and reimbursement. [P-AK]

So, I think as we understand the timelines and how they’re going to work with NICE, because supposedly technology, under ILAP should be taking priority with NICE, but then we know that NICE has only got finite number of meetings and the demand for them increases
overtime, so they need to fix that part of the equation. It’s not the MHRA which needs to upscale to handle all these regulated submissions. It’s also NICE being upscaled and I see more integration in the long run. This is where we’re going like more parallel discussions and integration. I could well even go and say that my personal opinion is that it’s going to end up being like PBAC to potentially in the next 10 years. The Australian regulatory and HTA agency. So potentially we’re moving towards that direction at some stage. [P-DN]

MHRA’s new working model (collaboration with other regulators, e.g. Reliance, Project Orbis), if implemented well, could expedite the regulatory timelines. Furthermore, the MHRA is shortening regulatory evaluation timelines to 150 days, which is shorter than the EMA’s regulatory standard evaluation timeline.

So, we’re in interesting times right in the post Brexit environment. In terms of licensing currently there is a procedure called reliance for MHRA which allows you to just recognize what the EPAR decision is and do that within 5 days but in 2023 that would disappear and then you’re in the situation where you’re just having to go to MHRA, but there’s an opportunity there because MHRA has 150-day process. This could potentially make it so you get your license earlier than NICE is ready to go so there could be a further delay, but you know it could also be the case that’s desirable. And because you could still be earlier than the rest of Europe. You can start marketing your product and then you’re applying pressure on NICE to make a decision because you’ve already got a license. [P-MR]

MHRA has the 150-day process and they’ve put in at the same time the Brexit agreement was being negotiated. And the whole design of that is to make it so actually, you completed all the hard parts before you even start the MHRA part. The EMA already asked questions, FDA probably already asked questions. You should have all the answers by that point, and it should make the process relatively simple, so that saves the MHRA labour... and potentially you can hit the same timelines or slightly earlier timelines. Which, like I said earlier, it’s all about where you are relative to other places’, so in that NICE miss the trick when they were doing their process updates. [P-MR]

Following Brexit, various initiatives have been introduced that encourage early and closer collaboration between regulatory, HTA, and payer bodies.

If you get through MHRA quickly and say follow the innovative licensing pathway that has been announced so if you could accelerate and go quickly through MHRA. And if you had confidence around, a positive NICE appraisal, then a good early regulatory assessment early positive, NICE appraisal and patient access in the UK could be very positive for other markets and you could start gathering real-world evidence as well very quickly after that and other data collection arrangements. [P-JS]
There is a drive to bring the medicines earlier to the UK than the EU. The UK regulatory body MHRA, which previously used to be the EMA rapporteur, has shown its agility during the assessment of licence applications for vaccines. Pharmaceutical companies need to allocate some additional resources as an additional licence application to the UK MHRA is required. Although the EMA requirements are considered more stringent than the FDA requirements, it is anticipated that MHRA could have an opportunity to move between.

*The FDA approves phase 2 data right single arm studies that would not be the case in the EMA. They do not like single arm studies, they need the phase three double blind study to approve with specific endpoints. The MHRA is probably going to flex in between and will allow you a phase 2 study pending upon additional data collection, and you know the new regulatory framework seems to start being built around that area whereby we might actually give you some flex with regulatory so long as the risk benefit profile is obviously favourable. But then we’re going to also allow you to collect the longer-term data to secure regulatory and HTA access further down the line.* [P-DN]

*Right now, there is no problem because we’re using the EMA procedures still or the end of the next year, but later on, we’re going to go into a fast-track regulatory process through the MHRA. What does that entail is that we need to have a separate regulatory submission dossier in the UK, that requires a huge number of resources. So, if you’re not prepared as a company to go ahead and do that because you’re a small company, then obviously there’s going to be a huge gap between UK approval and access to medicines versus other geographies. Now I still think that the UK will remain a key geographic area for the submission to take place. For example, it has proven its agility in the vaccines assessment, as it’s a very stringent regulatory authority, it’s like at par with FDA and that it used to be an EMA rapporteur.* [P-DN]

Parallel trade has been used to address medicine shortages in the United Kingdom. This also ensures that patients always have access to life-saving medicines. Parallel trade is expected to become difficult due to Brexit.

*I guess the big challenge is about parallel trading and imports and things that I don’t know. It’s interesting, but I don’t know what’s happened to the parallel trading market since Brexit, presumably that’s quite hard to do now.* [P-NP]
5.2.5 Medicines uptake post HTA recommendation

Positive HTA recommendations do not necessarily result in positive reimbursement decisions, as these decisions are made at the regional level. The degree of agreement between HTA recommendations and reimbursement decisions varies significantly between countries. The size of the uptake of the medicine is determined by HTA body restrictions, as well as local or regional restrictions.

Implementation timelines and delays

The NICE positive recommendation requires implementation within 30 to 60 days, but significant delays are possible. It is not only a matter of time, but this also depends on the level of implementation and the adoption of medicine. The implementation of anticancer medicines is quite quick.

*It depends on your definition of implemented, but if you have a definition that says at least one patient gets the medicine, you’re probably going to find implementation fairly happens in most places. If you regard implementation is that the medicine is available to the expected cohort in accordance with the indication. I think that’s going to be a little bit more challenging. Following HTA recommendation between NICE publication and adoption on formulary and adoption on guidelines and in Wales time period should be somewhere between 0 and 30 days. And in England that period should be somewhere between 0 and 90 days, but we have got examples of it being 200 days, 280 days, 390 days.* [P-TJ]

*In oncology, I would say it’s quite rapid. I’d say it’s gonna be 30 days and actually sometimes that can be immediate. For oncology medicines I’d say it’s between 0 and 30 days for implementation. For other medicines, it’s it can be up to 90 days.* [P-AK]

Although implementation is expected in a month or two, the Cancer Drug Fund (CDF) in England helps to implement HTA recommendations almost immediately while full funding approval is awaited at the regional or local level.

*Just kind of top of my head for cancer products it could be about a month or two that you would be looking and that you could also apply for that cancer Drugs Fund funding Kind of interim funding prior to it becoming available on the NHS in England so. From my experience is about one to two months. Where it might change is in like a ATMP products coming in and*
the implementation that is required of those advanced medicines compared to small molecules. So, you might see that you know pushing out, but I think what you're seeing with a lot of companies is that they're engaging quite early on. Companies that have assets with far advanced therapeutic medicines that I think they're trying to ensure that there isn't that lag between the access decision and actual patient receiving the treatment. [P-CD]

In Wales, there is something similar to the cancer drug fund. It helps pay for the use of medicines for 90 days after they are approved or until guidance has been passed on to the health board or trust level.

So, in Wales I cannot remember the name, but similar to the CDF they have some monetary fund in place for oncology medicines that funds their medicine after its approval for 90 days before it goes to the trust level. So, in those 90 days, whilst they're updating guidelines and trust that preparing to be able to provide access to medicine. There is a centralized funding similar to England, so it's very similar to the CDF funding in the same place they call it something different I can't remember the name, but it works in exactly the same way as CDF does which is to provide funding in that 90-day period before guidelines updated to ensure that accesses is uniform throughout Wales. [P-MJ]

Following a positive NICE recommendation, there is an expectation that payers should fund the medications within a 30-90-day period. But implementation is delayed for multiple reasons, e.g., further negotiation with payers or the NHS is required to agree on the terms or arrangements to manage the complexities of the implementation. No challenges are reported for implementation in Wales.

I believe there's a commitment to implement it after NICE recommendation not necessarily the constitution, but I believe there's a commitment to honour those 90 or 30 days I'm not aware of that it hasn't happened, but I guess there could be areas where there was some further negotiation or discussion with NHS England about how that implementation would work in particularly complex areas but I'm not aware of any specific examples. [P-JS]

In terms of implementation in Wales we have never actually worried about Wales from access perspective. Once you clear the HTA hurdle. I don't think there are any challenges with Wales, actually, there are a few places. I mean most of Wales tends to focus around maybe three or four key cities so if you are dealing well with those health boards. [P-Sk]

A positive SMC recommendation does not require implementation, but all 14 health boards are expected to make decisions in two weeks.
I don’t think they have a set implementation period like that because it depends. The Scotland SMC recommendation is not legally binding, so it’s just SMC advice, and then it’s up to the health boards in Scotland to decide whether they want to reimburse the medicine. [P-SDS]

Scotland doesn’t have mandatory funding in fields, but there is an understanding that all 14 health boards will adopt SMC decision within two weeks, so they received the draft guidance and in two weeks they implement it on their local formularies. They meet once every month, basically before the SMC public guidance is issued. We know what technologies are coming along because we notify them. [P-DN]

In Scotland, implementation timelines are not defined. In Scotland, implementation is relatively faster in big cities including Glasgow and Edinburgh. This is when compared to remote health boards.

It’s hard for me to be more precise about implementation time in Scotland. I think that in the big centres like Glasgow and Edinburgh, they can move quite quickly. As you go further, as you become more remote health boards, I think it can be a little bit slower, but that’s where I think the influence of clinicians who have maybe been involved in clinical trials is an important factor. [P-AK]

In Northern Ireland (NI), the implementation time frame is unclear. Sometimes NI follows NICE, sometimes SMC. Following Brexit, the implementation situation in Northern Ireland has become more uncertain. Implementation is delayed and challenging in regions with a larger population; for example, implementation in England is not as efficient compared to Scotland, Wales, and Northern Ireland.

Northern Ireland is a little bit easier because it’s a smaller population. I think the bigger population, the harder it is, or the more variety you get. So, I suppose it varies on population. It’s probably if you want something implemented in Northern Ireland and they agree to implement it, it generally gets implemented. But there’s only 1.7 million people, you know it’s a bit like saying, can you get it implemented in West Yorkshire? So, I think it’s probably population based. It’s harder to manage a bigger population. I think the same is true even in Scotland. They’ve only got a relatively small number of health boards and dominated by Glasgow and Edinburgh, so it’s fairly they tend to follow Glasgow. [P-PM]

My overall sense from kind of hearing from other people is that Scotland tends to be a bit more efficient implementation than England does. Perhaps that’s due to just the relative complexities of the health systems and the relative sizes of the different health boards. [P-FF]
Implementation Challenges

The size of drug uptake depends not only on the restrictions of the HTA bodies but also on challenges in implementation at the payer, hospital, and physician levels.

NICE has a very small implementation team. In the short term, this implementation team. Long-term solutions are through standardisation and digitalisation.

_Nice has an implementation team but it's only one person per region, so there's one person for the whole of East Anglia, one for London, one for the southwest now. I think anyone who's worked in the NHS will know that that's a really big span of work to do. In the short term, you could beef up that team. But I think the solutions are Standardization and digitization. and then everyone can see and then the public could see well [P-TJ]_

Regional health bodies or payers can put additional restrictions in place following the recommendations of the HTA bodies. Further restrictions could be due to multiple reasons, e.g., regional health bodies' assessments that there is a lower unmet need. Sometimes there are operational challenges that require further consideration and will impact the uptake of medicines.

_NHS England is separate entity from NICE and the challenges come in the form of the level of unmet need which NHS England or the CCGs see. If they perceive lower unmet need then they have the potential to put up barriers for utilization of drugs, so being available on formulary is not the same thing as being used by the patient for multiple reasons. One of the reasons could be that NHS or CCGs putting up artificial barriers for utilization. So, they need preauthorization of treatment if you want to use a certain drug then tell us why you want to use it and why you are not using something else that’s being there. There is something called commissioning guidance which is separate from NICE, and it broadly follows the NICE recommendations, but there are other elements that feed into it also, and these are usually the financial elements. [P-SK]_

Once you have your license, NICE can impose a restriction, but then NHS England can also impose further restrictions. So, they might say you can’t treat for longer than X number of years or we have a particular subgroup that we prefer and so we will exclude from the other subgroups. Then it is about get it out into the field and understanding the operational challenges. For example, in oncology your chair time different to your competitor which mean that you [AN: Physicians] can see more patients through…. So that is often a big driving factor that whether or not this treatment has been used before. Is there a lag time between learning how to use it? Are there any biomarker tests that need to be taken in order for them to have that treatment? [P-SH]
Regional bodies (CCGs and ICSs in England and health boards or other related bodies in other UK countries) have their own budgets and treatment guidelines. In England, the NHS pays for certain medicines centrally, but CCGs and ICSs are responsible for most treatments. Funding is not as centrally organised in Scotland and Northern Ireland as it is in England.

The way reimbursement works after NICE is certain drugs get reimbursed centrally by NHS England. So, NHS England pays for it, they are the single payer, whereas certain drugs are the responsibility for paying for them is not central with an NHS England but with CCGs or what’s now called ICSs. It’s done because for example, in certain diseases it’s the prevalence is high in certain areas and low in certain areas. So, to have that equitable care, NHS England has taken the responsibility and said that because it’s such it’s not a widespread disease. We are going to be paying you said rare disease. We are going to pay for it centrally whereas in some other cases like psoriasis or rheumatoid arthritis or diabetes, care is actually more towards the CCGs. [P-SK]

Scotland has around 6 health boards to implement while England has many more resulting into more heterogenous access within regions of England compared to Scotland. In terms of implementation of HTA recommendations Scotland is something similar. They have their local health boards and actually Northern Ireland as well, but I think because of the size of the population, it tends to be much more centrally controlled so you don’t have a level of complexity that you see in England. [P-SK]

Keeping in view the budget and unmet need in their individual areas, responsible payer bodies either reimburse all patients in line with HTA recommendations or introduce further restrictions. To implement the final decisions, local or regional bodies develop commissioning guidelines.

What happens is from their perspective, they’re looking at treatment costs per patient and the cost of drug is one element of it. There are many other elements like monitoring costs. Every time you give it treatment, you need to monitor the patient on a regular basis. But the moment you do that, you’re actually increasing the resource constraint on NHS. For example, some of these drugs can be taken only in the hospital, especially these high costs infusion treatments.... From their [AN: payers] perspective they’re looking is how much it’s going to cost me for managing the patient on this drug. So, companies have to make an argument for bringing that overall cost of managing the patient, cost per year and that’s why the metrics which CCGs and NHS England look at is slightly different from the metrics which NICE looks at. [P-SK]

At national level, if there is the NICE recommendation that is good. Usage of drug depends on the restrictions they had put. But then when we’re talking about a regional picture. the budget in the hospitals/trusts plays a role. If there are certain restrictions, if doctors don’t not
fancy medicine or they don’t support it, then we have also the guidelines that play around. Then if a drug is recommended by NICE, but it is down on the guidelines then that’s an obstacle. In practice, if there many other alternatives in a guideline that they don’t favour your drug. Most companies don’t stop just at the HTA decision they do also look in to influence guidelines or maybe there are also therapeutic protocols on the trust level. How to put the drugs in the formulary in the hospital. [P-VS]

Sometimes, despite a favourable budget impact assessment and NICE recommendation, the uptake of new medicine is poor. In one instance, this was attributed to a lack of interest on the part of clinicians and commissioners, who did not grasp the impacts of the new medicine.

I’ve definitely had some experience of a product which had a very positive NICE recommendation, but it wasn’t effectively taken into account by clinician. The recommendation couldn’t have been more positive. However, it was not a high-profile therapeutic area and but it was so positive that NICE did a budget impact assessment and they issued their guidance. PCTs could actually had saved money if they implemented the guidance and yet it didn’t happen. I think clinicians just didn’t quite understand the impact and the importance of the therapy area. Because it wasn’t necessarily life-threatening condition, but it was very much condition which made people’s lives quite miserable, and this treatment could make a big difference to individuals that I just don’t think it was taken seriously by the clinical community or maybe even by the commissioners as well. You need motivated clinicians to implement guidance. [P-AK]

In England, budget impact tests are used to figure out how much a new technology will cost the NHS in its first three years of use. If the budget impact is more than £20 million in any of the first three years, NHS England may talk with the company about business.

And the challenges to the implementation start from the fact when there is a therapy that is being recommended with a huge impact on the budget. One example that you can take, and you can analyse is the hepatitis drug from Gilead. So, this therapy was highly cost effective. It was basically eradicating a disease. Because this therapy had a huge impact on the budget and probably Gilead hasn’t, and I think in the words of the CEO of the previous year, or they didn’t do early engagement with the health care systems to prepare them for the big budget that required. However, if the impact on the budget is very high or higher than anticipated, that will be a barrier. [P-FT]

It is not just being cost effective, but we also need to make a new budgeting threshold so if you have a new innovative technology that is a new paradigm. And it’s not displacing an already expensive technology you need to prove that you’re not a huge burden to the NHS budget. For any of the first three years, so you know you must not break the £20 million
budget impact test in a first three years. So that's a key challenge, and it's a challenge because most new technologies that come to disrupt the treatment pathway and offer transformative benefits to patients basically, they will be associated with the costs. [P-DN]

In England, a budget impact threshold has been set, but not in Scotland and Wales.

Treatments that cost less and have little budget impact are easier to implement.

I'm not sure of any particular budget impact thresholds like specified for England in Scotland, Wales, but they do ask you to calculate the budget impact. Depending on which is calculated from the number of patients and the cost of the drug and the treatment and any additional costs of that treatment. If there was a really high budget impact in Wales or Scotland that would probably be taken into account in the decision making, but I'm not aware of any budget impact thresholds like there is in England. [P-ALS]

I would say and once again it can depend on the disease type, and you know the likely budget impact of your drug as well. So, if your drug is likely to have like a relatively minimal budget impact on the system, it can be a lot easier to implement, particularly if you're swapping out an existing treatment primarily for like a new treatment that there isn't like a massive net additional like cost or budget kind of implication for the system then that can be of more straightforward relatively. [P-FF]

In England, it takes around three months to set up a new drug treatment. Entry into formularies and obtaining an appropriate position in the formulary, the blueteq system, DM&D (the NHS Dictionary of Medicines and Devices), treatment protocols and guidelines, and stock availability are also the key steps in establishing a new drug treatment.

Getting on formulary is more difficult in some areas getting prioritized on a formulary 'because it's not just about being on the formulary it's about your position within it, whether it's your first-choice drug or otherwise. [P-MR]

DM&Di is basically something that you've got to get onto the ordering systems essentially in the hospitals. Like the first thing, it has to be available on those systems to order and then obviously then you've got to get onto the hospital formulary... And then probably the next step is to get it into the sort of treatment protocols for that condition so that the Commissioners will sort of specify particular kind of treatments. That can often be the hardest thing. because if your treatments positioned third or fourth line then then you've got a problem. So, there's quite a lot of work to do at a local level to ensure that your medicine is positioned sort of high enough up the treatment tree that you know kind of get access and patients can actually use it. [P-NP]

Part of the challenge, particularly with oncology drugs, is that you in order to get the reimbursement system that NHS insist on using is something called blueteq. So, blueteq is. computer system used for high-cost drugs that are funded by NHS England directly. So you know through specialist commissioning. The way that hospitals get reimbursed is they
basically have to enter the patient details and the indication into this blueteq system, and it takes about three months to set up a new drug on that treatment. So, there’s no way you know, even if you think you can kind of streamline the process, you can’t. It’s a very rigid sort of three-month process. [P-NP]

The setup and the readiness or capacity of hospitals or clinics to adopt new treatments are some additional steps for the establishment of new treatments.

The other barrier to the implementation, it would be something that has to do with the infrastructure. Whether for instance to use new therapy the hospitals require certain level of equipment level or a training. They require to massively change the pathway, something that has to do with the infrastructure. I would say the number one thing is the impact on the budget. That’s why now they have the horizon scanning and every two years, let’s say if we have a therapy in the organization I’m employed and will have a therapy that is to be launched three years from now. I been asked what the likely positioning for this therapy is, what will be the prevalent population, the incident population. So, the manufacturers are kind of obliged to give this data to the horizon scanning to prepare the NHS to prepare for certain innovations. [P-FT]

If a drug requires a new service to be in place, and or NHS has to reshuffle or revisit their services. It’s a challenge for the system because it takes time, so the uptake will be slower. Second one that I can think is the capacity of NHS England. So, we have seen in different disease areas there are no people in certain places who can for example operate some assessment infrastructure. So, patients cannot be a let’s say examined because there is either no machine there or the person to operate the machine. [P-NL]

The NICE recommendation requires new treatment funding, but any related diagnostic test or biomarker test requires additional funding at the local level.

Only the tag program in NICE is mandatory so be technology appraisal guidance for the drugs, so the diagnostics. For example, they can be appraised by NICE. They don’t have to be appraised by NICE, but if NICE recommends diagnostic test, then the funding is not mandatory from NHS budget, it’s the local CCGs that need to fund it. You can have a situation whereby a drug with a biomarker is approved. The biomarker was assessed by NICE and is approved. So, the patient eligibility is assessed based on biomarker test but then if the test is not established in the NHS setting. Either you have to convince the local authorities to pay for the biomarker test or try to come into a commercial agreement between them that we will fund the biomarker test so that you can identify the eligible patients and open access to your medicine. [P-DN]

Medicine uptake is also dependent on type of medicines e.g., treatments for rare diseases, unmet need, competitive landscape, geography (urban & rural), New molecule or new indication, category of medicines, restrictions at Physicians level.
Historically, negotiations with payers began after the HTA recommendation, but now there is a drive to start this process early.

*I think you have to think about it as if they are not together, you have to think about them as separate parties with separate interests. And it’s the three of us that come together to try to negotiate this. Once NICE do their thing then all three of us come together to try to negotiate the price and to negotiate how to move forwards even though they do keep an eye in the background. I think usually it’s at the end, that’s when they come in and say this is what’s going to happen.* [P-NP]

*NICE will say that they don’t negotiate on price, so they just look at the price that they’re given. But what tends to happen is it’s more NHS England who actually does the negotiation in England. So, what will happen is that that NICE will sort of tell the company. Well look you know from what we’re looking at that price you’re not cost effective. And then they’ll refer them to NHS England and NHS England will have the discussion about what they think is a cost-effective price based on like the number of QALY gain. Sometimes I will go back around through NICE again, other times and NHS England will kind of just say yes, we’ll agree to this and that there’s a bit of an informal agreement between, NICE and NHS England.* [P-NP]

The uptake is also dependent on the type of medicine, e.g., treatments for rare diseases, unmet needs, competitive landscape, geography (urban and rural), new molecules or new indications, category of medicine and restrictions at the physician level. Implementation is more challenging for non-oncology medicines than for oncology medicines.

*It’s very much dependent on the drug and it’s because if it’s something in a rare disease where there’s no other treatment and it’s a really innovative therapy. I worked on a drug for, mesothelioma it’s a brand-new immunotherapy. It’s never been available before, so as soon as that is available, every single clinician would know that that was available, like you wouldn’t have a problem with implementation. So implementation for those drugs, if it’s a higher unmet need not have problem. Whereas you know asthma drugs where there’s lots of other treatment options implementation would depend often on the industry like sales reps to be going out and you know they have to get their marketing material ready, and they have to be going out to their clinicians and respiratory teams and promoting their drugs.* [P-ALS]

*Hospitals have to implement the NICE decision, but in practice there’s probably always an alternative medicine out there. Unless it’s a completely sort of unique product, there’s probably an alternative sort of treatment out there, even if it’s off license. So essentially, unless you’re like going to be competitive against whatever is already been being used then you’re still going to sort of suffer due to slower or reduced uptake.* [P-NP]

Compared to remote rural areas, medicine uptake in large urban areas is relatively faster.
I think the challenges will vary by locality, inevitably and there will be some places where the challenges are always exactly the same or do not vary, like when you look at large urban centres, chances are it is going to be the same implementing things each time.....But if you are looking about more rural locations or things like that. There could be challenges with getting everything implemented. [P-MR]

Although the NICE evaluation period for already licenced medicines with expanded indications remains the same, the rate of uptake has accelerated. This is due to the fact that the drug already has an established safety profile and is listed in formularies.

If you’re going through regulatory procedure and you already have a license in one area, and now you’re expanding your indications., that’s faster. But if you go through NICE, the time to implementation is exactly the same. Whether it’s a new indication or new molecule. It’ll vary by what process you go through. So if you go through a fast track appraisal you get 30 day implementation. Everything else is 90 day and that doesn’t really make a whole lot of sense. Because after you’ve got that first indication, usually you’ll have established what most of the safety information as and what you expect to happen, it’s already on formularies, so there shouldn’t actually be a huge challenge that would make it take 90 days to implement. And to get the thing on formularies for the new indication it should be faster than that. But that’s not currently in the rules. [P-MR]

Implementation is more challenging for non-oncology medicines than for oncology medicines. The availability of interim funding for cancer drugs is one of the reasons for the faster uptake of oncology medicines.

when NICE says yes, there is funding in place for oncology medicines, so I suppose in terms of carrying over, I think the challenge might be more for non-oncology space. For oncology specifically it is just the typical things which is uptake Physician choice was for. Physician is used to, and of course you know how not having several competitors within the field and always having something new coming up and physicians always try a new product aside from the typical market economics, I don’t think there is a there is a huge problem in oncology space in terms of, you know, implementing actual decisions that have been taken on board from NICE. [P-MJ]

GPs and consultants follow the commissioning guidelines of the local health body.

Historically, local restrictions were not as transparent as they are today.

Everybody knows if you place a local restriction on a medicine. The GPS will generally not push back against it, and similarly consultants will conform to restrictions that have been put in place. Now normally those restrictions are transparent. There is a commissioning policy. But increasingly over certainly my careers, you know, through the late 90s and up until 2020
the. Some of the cruder restrictions around implementing were stopped being used. I remember they used to be with some biologic medicines that the consultant could only prescribe it for 10 patients, and he could only prescribe another patient if one of the 10 on the medication died or whatever. [P-TJ]

**Suggestions to improve medicine uptake**

The interview participants made suggestions to improve the uptake which include early engagement with all stakeholders (payers, physicians, and patients), pharmaceutical companies to understand how treatment will affect overall service and to influence treatment guidelines, therapeutic protocols, and entry into formularies.

So, anticipating early and engaging with the system to kind of make them firstly aware of the upcoming challenge and then a help working with them to help shape the service in a way that it’s going to be more accommodating to the treatment. It’s a common strategy that’s used and pharmaceutical companies do tend to partner with local health bodies in order to help that as well. I think one of the main barriers to it is communication. Understanding in terms of how in what ways your treatment is going to overall impact your service. You may just be looking at the, immediate kind of costs of implementing, but you may not necessarily be thinking of downstream savings on other services and other resources that could end up actually being more favourable in the long run for you to implement. [P-FF]

I guess getting out there and making sure that the clinicians and all the staff are kind of trained and or kind of ready to implement the medicine as well, so making sure that they know kind of what’s the process of like what pre monitoring you need to do when you need to give them medicines, what post monitoring, have they got a service that has capacity. I guess helping with that whole infrastructure set up is an important step as well. Service Readiness is really important in making sure that, I guess while the HTA processes going on the those that are involved from the pharma company and from NHS England or NHS trusts are kind of taken on that journey as well simultaneously so that they know what needs to be ready so that as soon as it got the positive recommendation you can launch. [P-KN]

**Medicines uptake without HTA recommendation/ negative HTA recommendation**

According to interview participants, the ineligibility of some products (such as HIV therapies) to go through the HTA process, the high HTA body fees and other associated costs to prepare submissions, and the strategic choices were cited as the most important factors for the absence of HTA recommendations.
HTA is the gatekeeper, and it is more difficult to get reimbursement through other routes.

The HTA recommendation is a must for routine commissioning.

In a market like the UK, where the HTA is the gatekeeper, without it you cannot basically function. In other markets like the US, it’s a different situation, but again that’s changing over there as well. You have to pay for HTA at NICE, it’s a fixed cost. There’s also a fixed cost that will be associated with developing HTA submission. I think developing a HTA submission might be costing anything of a quarter of a million plus staff hours. That’s probably adding it up to half a million pounds, potentially just ballpark estimate. If you now go to NICE and you make a submission, it doesn’t mean that you’re going to be 100% successful, but I will just give you a success rate of 67% you can see their KPIs on their website. [P-DN]

I think Scotland is much more restricted and it’s less flexible [AN: less flexible without HTA recommendation] on having deals and agreements on local setting. So yeah, it’s much more difficult for companies. I would say it’s much more restricted in Scotland. The companies have to go through SMC. There is not this flexibility like NHS England or NICE. [P-NL]

In case NICE has not selected your product for evaluation, or due to NICE’s limited capacity to review all medicines, or if the indication is too small, one can just go straight to NHS England. Historically, there are some categories of drugs that do not have to go through the HTA process.

Historically there are products where there was no requirement to go through HTA, so I believe the HIV drugs in the past didn’t go for HTA approval so they’ll be certain categories that will not have been assessed in the past. [P-JS]

NICE don’t have the capacity to review all the products so they review thing that they say have a have an impact on their budget so they would not choose for example if the indication is too small. Kalydeco is one of those examples of our product. NICE, never review the product because it is only affecting like 400 patients in the UK so there is a special committee and there are there other special like cancer products as well that you can also reach an agreement before NICE review to have a specific fund for cancer drugs and then you go back and review the data later. [P-TH]

Mechanisms of access to medicines in case of negative or absence of HTA recommendation

As shown in the following, qualitative data discuss access to medicines mechanisms in cases of negative HTA recommendations or the absence of HTA recommendations.
Payers can overturn negative recommendations. Negative recommendations can be overturned by means of a new pricing agreement or data collection agreement.

*It's always been one of my ambitions to turn a national no into a local yes. But I don't believe I'm aware of that. I think the system is pretty tight then that the influence of NICE is strong. I think NHS England could take a challenging HTA submission and just turn it into a managed access agreement. But I think without either of those things and I don't think it happens if you get a negative. I think you have to think you have to go back and turn that negative into a positive with new data or new pricing agreement or whatever it might be. [P-AK]*

*It's a good question and negative HTA actually again CFTR modulator provide a good example. Although it has access to all the CFTR modulators, so triple, Symkevi, Orkambi®. Orkambi® was submitted 2015 appraised 2016 received a negative recommendation, but as currently reimbursed, through interim access agreement. Outside of that I'm aware of most products would have gone through unless there's some historical ones. Actually, Kalydeco as well didn't go through the HTA. That was the clinical commissioning agreement, but from 2017 onwards they were very, very few. [P-CD]*

The HTA process can be averted or delayed through new pricing and / or data collection agreements, clinical commissioning agreements, value-based agreements, value-based partnerships, and agreements at the local level. Recent examples of these agreements are related to Gilead and Novartis products.

*Clearly there are some vertex examples from 2019 and 2020. And I think there's a quite recent example that spinal muscular atrophy drug that was funded by NHS England about three months ago. And I don’t think that went through a NICE process. It was certainly more, formal wording being proposed, which would suggest that for some products they would be not looked at by NICE but handed straight across to NHS England to make more of a value judgment. And have a negotiation rather than a formal health technology assessment so I think we might see more of that happening. And so, which would be interesting to see how that develops. [P-AK]*

*I think there are with some of the CAR T products that came through from Gilead and Novartis, I don't think they went through a NICE appraisal. I think that was again a direct negotiation with NHS. I don’t think for these highly specialized medicines NICE, highly specialized technologies path is sufficiently supported. Obviously, number of people complaining that single technology appraisal process at NICE isn't sufficiently robust for rare disease medicines. So, unless you’re an old drug and ultra-orphan product, you got no chance of getting into the highly specialized technologies pathway at NICE. Which means that you end up in the single technology assessment. [P-AK]*
The HTA process can be averted in exceptional circumstances. For example, COVID-19 medicines do not have to go through the HTA process.

I guess a recent example could be COVID medicines. I know because of their role in the pandemic that kind of rapid and system to get them through, which is understandable. Obviously, then like very low-cost medicines as well don’t have to go through HTA recommendations. [P-KN]

So, you may have the situation that a patient doesn't have options other than the one that's not recommended. You know, and in that situation would you say this patient gets nothing? No, you would make an exceptional application to fund the medicine. You know, so if something is deemed to not be cost effective, it doesn't mean it can’t be used and it could be used in a number of different situations. So could you be used either through that exceptional application where you have to apply for local funding to fund the intervention or it can be used in clinical trials, so there may still be clinical trials out there, in which case people get the medicine, it’s just not routinely commissioned. And that’s the key the HTA recommendation is for routine commissioning. [P-MR]

In the absence of HTA recommendations, individual funding requests are another mechanism for patients to access medicines.

If you get a negative recommendation so it won't be reimbursed, but patients could still have access, so you’d have to do an individual patient request if it’s something like a rare disease and it was still proven too high for NICE and a clinician thought that patient had definitely had a need they could apply to their CCG or in Wales or in Scotland they’d apply to their health boards and it would be a clinician led individual patient funding request for that drug. So that’s for particular things like rare diseases. [P-ALS]

Most Commissioning bodies have tightened up their procedures so that it’s very difficult for a patient to make that application. They have to have a qualified clinical professional to make it on their behalf, so their GP or their consultant would need to do that. It’s more commonly falls on the consultant because the GP will normally claim it’s out of his or her professional expertise. For the consultants I know anecdotally, I can't prove this filling in an individual funding request is time consuming. Takes quite a lot of research. So, for the consultant to do that they have got to be convinced that this is the treatment that this patient needs, and there’s no other available treatment, so from that point of view they’re fairly rare. [P-TJ]

Interim access arrangements or interim funding in England and Wales CDF for oncology medicines and IMF for non-oncology medicines are two examples. Due to these interim funding arrangements, if the pharmaceutical company is able to agree on a lower price for
In this interim period, it is a win-win situation because the NHS provides access to the patients and the pharmaceutical company has the opportunity to collect data from the real-world environment and generate revenue. Scotland was less open to having deals and agreements outside of the HTA review.

I think the Cancer Drugs fund. It is a big one. So, where there's uncertainty in the data and especially if you're coming to HTA with data, that's not enough of it or it's not mature enough and then to have a route to access is very positive, so it's the Cancer Drugs Fund and there's talk of an IMF, an innovative Medicines fund which would mirror the Cancer Drugs Fund but be for broader than oncology medicines and that's due to be consulted on soon, so that's one area as well. [P-JS]

So apart from NICE then you have cancer drugs fund and Innovative Medicines Fund. So, these patients, they have early access to potentially life saving medicines. Before the any reimbursement decision you can access these drugs. But then they review the information, at some point. And that is good because it reduces the time it takes for the access and for their reimbursement That's also for rare diseases. So, it's not only for oncology product. It's an extension to the cancer drug fund. [P-VS]

If medicines are not routinely reimbursed through the public health system, private insurance is another mechanism for funding the new treatments. For example, the Novo Nordisk antidiabetic drug, ie, GLP-1, is funded through private insurance. An estimated 9 or 10% of the U.K. population has private voluntary health insurance, and this private insurance market is growing.

But the general kind of requirement and the way things still stand is that for the vast majority of disease areas, NICE have to review and then either approve or not approve the medicine, and if they don't approve it, then they won't be routine funding on the NHS. It doesn't mean that it won't be accessed by any patients at all, because there are still private funding mechanisms, like through private insurance and the private insurance market. The private market in general in the UK is growing at the moment I. I think it's up to about 9 or 10%. currently. [P-FF]

I mean if it's negative with NICE, then it's very likely that NHS will not pay for and if it's not being paid for, if you could prescribe it, you don't get the payment that you need in order to reimburse this treatment. So, it wouldn't be available for routine prescribing unless covered through private insurance. [P-SH]
The Early Access to Medicines (EAMS) initiative aims to provide patients with life-threatening or severely debilitating diseases with access to unlicensed treatments when there is a proven unmet medical need. However, later in the process, there is no major advantage in terms of dealing with NICE, except that we have some real-world evidence at the time of HTA submissions.

*If I have a product that has gone through EAMs. It doesn’t necessarily make my life with NICE any different as the entire process is still the same. There is no advantage except for maybe getting a bit of real-world data. There is no advantage. Now the issue is EAMs from a manufacturer’s point of view, is letting you submit s and getting the product early into the market, the patients are able to get access to the medicines much earlier even before they are getting the regulatory submission. So that’s the theoretical advantage. Practically speaking, I don’t have any as from my perspective, as in from a pharma companies’ perspective EAMs doesn’t give me any advantage with NICE.* [P-SK]

5.2.6 Access to Medicines Challenges in the UK

Qualitative data in Study 02 reveal a number of challenges and barriers to medicine access in the UK. Key themes and related qualitative data are described below.

**NICE HTA process/methodology**

The key reasons for this challenge were strict reimbursement criteria and a lack of flexibility in the HTA system, particularly around ICER thresholds and HTA process evaluation timelines, the risk-averse nature of the system, the unwillingness of NICE committees to make decisions in the face of uncertainty, labour-intensive and costly processes, and the cost per QALY mechanism.

**Pricing of medicines**
The pricing of high-tech medicines and the implementation of complex value-based pricing schemes were also considered other barriers.

**Data Packages**

The availability of less mature data, the requirement of long-term data, divergent requirements of HTA bodies, and the generation of evidence for rare and ultra-rare diseases were also classified as barriers.

**Transition following Brexit**

The Brexit-related challenge was more related to the uncertainty of the regulatory process, the harmonisation of regulatory procedures, and the risk of delay in licence filing.

**Pharmaceutical spending**

The impact of COVID, its budgetary implications, an underfunded NHS, affordability and transactability were also discussed as barriers.

**Inadequate capacity of the healthcare system for medication uptake**

Precision medicines, infrastructure and specialist services to administer them, local adoption, a lack of well-defined clinical pathways, and more hurdles for non-cancer drugs were some other barriers, which were reported.

According to qualitative data, other key challenges include human capacity and resourcing, global access decisions, non-uniformity in decision-making, the government’s drive to establish the United Kingdom as a centre of innovation and access, the quality of the clinical trials, and digital healthcare.
The qualitative data findings for the challenges and barriers to medicine access in the UK are reported below.

**NICE HTA process/methodology**

The participants believed that the HTA system is out of date and incapable of appraising and assigning appropriate value to high-tech medicines such as CAR-T therapies, gene therapies, Advanced therapy medicinal products (ATMPs), and treatments for rare diseases.

Additionally, the current HTA appraisal system does not take into account the social care aspects.

*So, the key challenge now is that we’re moving towards more, innovative therapies, pipelines, and more targeted medicines and combinations of medicines. Simply the HTA process methods cannot handle that very well. Unless we fix that part of the system, the patients in the UK might actually not benefit from the best therapies out there and you start seeing that disparity, so that’s a key challenge.* [P-DN]

*One other thing is how you can also incorporate social care aspects.... They don’t count this social care aspect in a NICE appraisal because those two budgets are different. In my view they should also be accounted for because at the end of the day, if you are doing better and because you take a mental health pill and then that means you know you can go back to work. You can put more to welfare; you can be an active participant etc. That should be reflected into the value appraisal system.* [P-FT]

Companies find it challenging to successfully navigate the NICE process for new medicines that are not considered breakthroughs, and their market is already crowded.

*Challenge is how to prove the value of products because as we are moving now to medicines that they lose patents. e.g, in the antibiotics we need more antibiotics but at the same time most of the diseases have an option is a challenge to prove the value of your products and to have to gain positive recommendation. If you don’t have a breakthrough product, it would be more challenging to prove if you are in a very crowded for example, there’s so many psoriasis Drugs.* [P-VS]

The NHS in England uses highly specialised technology (HST) evaluations from NICE to decide how to use new and old highly specialised medicines and treatments. The current entry
requirements for HST are very strict and they prevent people from submitting some new
treatments that would be rejected by the standard technology appraisal (STA) route. This
makes it harder for people to get the medicines they need.

How do you select the topic, and which route you would go to, whether it’s a single
technology appraisal or the highly specialized technology appraisal because of the
differences of the threshold, I think there is a lot of challenge and NICE needs to understand
that. I think it’s a main challenge for the pharmaceutical company and NICE needs to adopt
it. [P-SR]

So not just a specialty product, but rare diseases and how to assess those properly when HTA
is really set up for small molecules, for standard chronic conditions and specialty conditions,
but not rare diseases. And there’s a gap between the STA process and the HST process. Those
to me are the two things that are going to be the biggest challenge. [P-AK]

Even considering recent changes to NICE methods, participants were not hopeful that they
would fully address their concerns.

If we spoke about some of the changes to NICE methods, I strongly suspect that it won’t be
sufficient to address some of the complexities that are coming in the future. Take the
example of a treatment like CAR-T, which is a highly individualized personal treatment that
you bear all of the costs for upfront and it completely goes against the classical
pharmaceutical model of a patented period where you accumulate revenue over time in that
10 or 15 year period of ongoing kind of administration of a drug. For a defined time it’s like
it’s a one off treatment that could, potentially curative, but you implement all the costs up
front, so from a cost effectiveness and modelling perspective, that is a difficult thing to
translate.

I don’t think NICE has kept up to date with their methods with the evolving technology. In the
medicine world, there is too much focus on apples-to-apples comparison, but you can’t do
that when technology is evolving. And the way you look at disease itself changes, but NICE
actually is refusing to, you know there because they want to compare with something they
have done previously. stick to the previous methods, which is not right. So, they need to
evolve. I would say updating their assessment methodology is the biggest challenge right
now. [P-SK]

NICE’s strict reimbursement criteria or a lack of flexibility in the system, particularly around
incremental cost-effectiveness ratio (ICER) thresholds and the cost per quality-adjusted life-
year (QALY) mechanism are considered a barrier for access to medicines. In countries with
more developed HTA systems, HTA bodies were willing to accept higher ICER thresholds compared to NICE in the UK.

One of the main challenges is the lack of flexibility in the system. Currently NICE have a threshold of between 20 and 30K for products that go up to 50 for end-of-life treatments and the cancer space. And then you've got the highly specialized technologies which only applies to a limited number of products that go through the system. That was like the case back in 1999 when NICE was set up and it still is the case today. It hasn't really changed, whereas the landscape and the products and the innovation that have happened over the last couple of decades, we're seeing completely different products coming through particularly around cell and gene therapies. ATMPs CAR-Ts it's just about, is the system ready for that? NICE are trying to address a lot of this with the methods review. But is it going far enough I don't think so. [P-CD]

In terms of the challenge for HTA in general I would say is using the cost per QALY mechanism. We have to model based on whatever data you have and you bring all of that information together and you have to bring sometimes maybe the comparator you looked at when your clinical trials going on. Because of the fast-moving landscape in oncology for example that comparator may no longer be relevant and therefore when you start to model the comparators are different, your endpoints are different and it's very difficult to synthesize all that evidence and make it to make sense. I think we need to start being a bit more flexible in terms of the economic principles that we use to make decisions because not every situation will fit in a cost-effective cost utility. [P-MJ]

The NICE evaluation process is well defined, but it takes 1 to 2 years and, in some cases, even up to 3 years to complete. This duration depends on the number of committee meetings needed during the review of the HTA submission package.

I would say the timelines for the evaluation because it if you think out of the box and you just zoom out the whole NICE process. For example, it takes around 1 to 2 year to be completely, which is a long process and if you have to go to a second committee meeting then there is additional delay and you have also the 90 days implementation period. So, I would say it's through the years basically almost 3 here. [P-NL]

I think having a clearly defined HTA. submission and approval pathway and time scale for that. [P-PM]

The challenge would be around, you know, just the practicalities of the delays that you know, and the time frames taken up. [P-NP]

The risk-averse nature of the system or the unwillingness of NICE committees to make decisions in the face of uncertainty is another challenge.
I would say the risk averse nature of the HTA system, and particularly the NICE committees, their unwillingness to maybe make decisions in the face of uncertainty. It’s a barrier to access. [P-NL]

The NICE submission process is labour-intensive due to the number of hours needed to prepare a submission package and then to respond to NICE requests during the review. Additionally, the fees associated with HTA submission are high. So, in some situations, the labour-intensive nature of the process and associated fees become a barrier to access to medicines as companies decide not to submit.

The NICE submission process is very robust and thorough and if you do get a positive NICE recommendation, it’s used across Europe but it’s a very labour intensive to do NICE submission. So, if companies can avoid that and go through get reimbursement through other ways, they will avoid a NICE submission because it’s not only takes up a lot of time, it also costs. £126,000 just to submit to NICE. So the cost of NICE submission process can be a barrier with funding and resourcing, but then it can be a benefit far reaching beyond the UK. [P-ALS]

I think challenge is resourcing. I think the process for HTA is already quite extensive. I know if pharma company is expected to pay for NICE submissions, and I suppose that helps, but we do find that in terms of, for example, you know the use of evidence review group. So they have different standards as they have different evidence review groups..... So, I think that’s another challenge in terms of resources. I think the more in-house we do it the more, the more likely it is to be consistent. [P-MJ]

**Pricing of medicines**

The pricing of medicines, particularly high-tech medicines, is another challenge reported in the qualitative data. Due to the higher development costs for specialty products such as gene therapies, these medicines are being priced at levels considered unaffordable to payers. Although companies expect to be compensated for high development costs, they struggle to persuade payers to pay for these new treatments. To address these challenges, complex value-based pricing schemes have been introduced, but due to the complexity of these schemes, there are challenges in their implementation.
I think one of the things that is potentially interesting is more around the potential implications for gene therapy when we might be looking at one off treatments. So how do you price that? How do you persuade somebody with a 12-week study that you're going to produce a cure for one year and ask them to pay for that cure. And I think there's some evidence from the recent Bluebird bio experience where they were talking about buying bonds over the different NHS financial years..... So, I think there's something there which I believe is going to be a massive challenge. [P-AK]

Pricing is another major area and not just in terms of companies being able to offer prices that would facilitate reimbursement but also practical barriers and challenges for implementing. We need to know if the system is set up well enough to capture data required to monitor complex pricing schemes, for example, risks sharing agreements or outcomes-based pricing mechanisms or pay for benefit pricing scheme. Is the system setup or is it overly burdensome to kind of collect the data and monitor and to calculate those rebates, all those discounts? If it's based on outcome, I think that's both the challenge and opportunity for the industry to facilitate more access, but at the same time, a challenge to implement. So, working with all the stakeholders to try to flush those different schemes out and get that implemented and get it signed off is a real challenge for pharma companies. [P-F]

Data Packages

It is a challenge to generate a data package that is not only enough in terms of size but also fits in all settings, e.g., clinical trial settings or economic evaluation settings. The problem of not having enough data is made worse by the fact that different HTA bodies have different data requirements and different ways of gathering evidence for rare diseases. So, it is hard to come up with a set of data that is acceptable to all the HTA bodies.

So, number one challenge is definitely I would say is data. Data snap is never perfect, and I think it becomes very difficult when we're looking at cost effectiveness because we're looking at it from a cost per QALY perspective. We usually don't have the data that fits perfectly the PFS and OS. When you start modelling, you're simulating real life. Modelling is not real life. You're trying to simulate real life, as sometimes data might fall apart because it's perfect in a clinical trial setting, but if we translate that data into an economic evaluation becomes a lot more difficult because it wasn't designed to be put into model. [P-MJ]

Since companies are going to HTA bodies, e.g. NICE, earlier, submissions are based on less mature data. This data gap adds more uncertainty and complexity to an already complicated process. Pharmaceutical companies address this challenge through some interim access
arrangements, for example, the cancer drug fund, with a commitment to generate additional data to address uncertainty or gaps in the data.

*I think the data packages and manufacturers potentially going to NICE earlier with less mature data packages or all because you don’t have the numbers of patients for and what would traditionally be considered a robust clinical package. And managing that uncertainty is going to be a big one because that that brings a lot of risk and complexity with it.* [P-JS]

*In oncology, the data is often immature, and we are expected to go when there is no data. Because we have the CDF in oncology, you can go early and enter the CDF, you can collect data. You could offer a different discount which is greater than what is the baseline. But then you stop being a comparative for your competitor who might be coming within the next six months. Obviously, if you could make it you want to make it baseline commissioning, but if you don’t have enough data, what do you then do? For example, if your competitor came and there was end of life at the time of submission. If they submit and take that end of life and the standard of care is better and there is no more end of life. How do you that? Because the fact that you’re 20 to 30 K ICER when they came and had a 50K ICER.* [P-SH]

Pharmaceutical companies find it challenging to address divergent requirements and long-term data requirements of HTA bodies. To address this challenge in some regions, companies navigate this complexity through interim access arrangements.

*Then another key challenge that we have, and it’s been faced in NICE, is that we’re always being asked for longer term data. But you know that comes, then it will be expensive rapid access. So, the CDF was used, or the new Innovative Medicines Fund is around that, like giving you access quickly enough when you don’t have the longer-term data. When NICE says long term data, they don’t mean like two years or five years. They mean ten years or 30 years. And then we just start to think, whilst it’s very important from a decision point of view, it’s frankly not realistic to run a clinical trial for five years or ten years or 30 years when it comes to like acute conditions. So that’s something else that needs to change. There needs to be a balance between how you assess uncertainty and how you’re able to quantify it and be able to make accountable decision with the amount of uncertainty still remaining that we want the drug or the technology or should be saying will be introduced into the health system.* [P-DN]

*I’ll say one broad kind of challenge is your evidence package increasingly, we’re seeing this divergence between requirements for licensing and requirements for HTA bodies.* [P-FF]

Evidence generation for rare diseases and ultra-rare diseases infrastructure to collect real-world evidence is reported as another challenge.

*For the future, I suppose, there is need for a wider network of real evidence. I think countries like Denmark and Sweden have really good registry, registry data and even Germany I think*
they have really good registry data. I think in the UK or more focus on things like that in the UK would be really helpful in the future. Pharma companies can fund clinical trials and real-world evidence data, but usually the point of which you want to submit it might be a bit too late. I think it will be more difficult to prove efficacy as well as cost effectiveness just based on clinical trial alone, so it's looking into how we not only use real world evidence, but also how we implement it in our models. Maybe we should start, using comparator arms for real world evidence rather than or randomized control trial. [P-MJ]

I do think NICE is heading in that direction. NICE announced very recently a new partnership with a company called Alicia to look at real world evidence and how it can be implemented, and at which point we should be collecting and how using them in HTA appraisal. So I do see a trend in that direction and I think in terms of access that will make a big difference between waiting for randomized trial which will go on for seven years to get overall survival or using a single arm trial which will be very small patient numbers but the RWE that is actually very useful to back up the data. [P-MJ]

Transition following Brexit

Uncertainty about the regulatory process and the harmonisation of regulatory procedures following Brexit are reported as another challenge for access to medicines in the UK. There is a risk of delay in licencing filing as regulatory responsibilities have moved from EMA to MHRA.

Challenge is the transition, what will happen when and it would take a turbulence in the industry in this country. As we move outside EMA, they might have uncertainty with regard regulatory processes. That might be an opportunity for regulatory alignment in general. It just seemed to cut bureaucracy in general. They should be benefited more from moving outside the EU to make the procedures more flex for them. And also, I see that the clinical trial regulation because they will need separate, probably. In general, all this harmonization of regulatory procedures is a challenge. [P-VS]

Another barrier is the additional step of the MHRA license now. It’s an addition. So, the regulatory submissions are often done by a global team, so they’re often submitting to the FDA and the EMA, and they get questions back. And now they’re going to have to submit to the MHRA as well and that’s a huge additional burden. [P-ALS]

Pharmaceutical Spending

Pharmaceutical spending budgets are limited, and this has been further impacted due to COVID and an underfunded NHS. These limited budgets present relatively bigger challenges.
for high-priced medicines and medicines for rare diseases. Although there are ways to overcome the barrier to accessing high-priced medicines for rare diseases in Scotland, it is difficult with NICE.

Budget and then this spending into pharmaceuticals is a challenge and will continue being the challenge. [P-VS]

Then the limited budget. Probably they will have more money for that yet, but they were coming also in a post COVID era, and you can see that the budget is scrutinized. [P-VS]

Scotland have some additional flexibilities within the system for orphan and rare diseases which NICE don’t have. I think there’s budgetary implications in Scotland which can be a hurdle, and that’s something to consider. Particularly when we’re looking at these newer products that come with quite a high price tag, so you know it can be more on the affordability side of things that could limit the access. [P-CD]

Well, in general there is a limited budget. Budgets are not unlimited. So, budget would always be a consideration. So, it’s about getting the most cost-effective medicines to patients, but also that the health system can afford it so that affordability is always a criteria. [P-SDS]

The affordability and transactability of medicines is a challenge for UK payers, such as the NHS and regional health bodies, due to limited budgets.

We haven’t really covered affordability because that’s a hurdle. And then you’ve got the cost effectiveness piece and then the transactability. So, if you’re trying to address the affordability with some complex outcomes reimbursement scheme and that’s just too much for administration and complication for the NHS to manage. It’s not a good deal for them, so I think those two other elements, affordability and transactability. When you can be highly cost effective, but if you’re going to completely blow the NHS budget it’s not going to work. [P-JS]

I would say a huge one challenge is going to be affordability and when you look at the rare diseases, I’ve heard for many years rare disease is rare. But when you look at all the rare diseases, they are not rare. The system can’t afford to fund highly expensive treatments for all the rare. So I think that affordability and matching the funding to the value that medicines is a very difficult one. [P-JS]

Human capacity and resourcing
Due to the scale of medicine's development, human capacity and resourcing have become even more difficult challenges. Due to this lack of capacity within the healthcare system, the uptake of medicines has slowed down.

Resourcing, come as a big one not only in pharma companies but also HTA bodies and healthcare systems to implement as well. We’re seeing an exponential increase in numbers of technology being submitted and NICE resource aren’t sufficiently increasing at a proportional rate. They’re trying to make efficiencies in the process, but it doesn’t always kind of work that way. You often see appraisals being kind of rush through committee meetings or having to have multiple meetings. I guess there’s an additional burden now with the NICE submission fees, that is a challenge for smaller companies. It might end up with companies not deciding to submit at all. It takes a lot of work to develop a submission to NICE and for companies to have sufficient resource. I think that’s another major challenge that’s often overlooked by industry and by regulatory bodies and HTA bodies. [P-FF]

Well, the first challenge is the resource constraint which is delaying the submission timelines. [P-SK]

In general, a big challenge is human capacity and resources. [P-VS]

I guess yeah, maybe the lack of capacity within the healthcare system to actually implement uptake of medicines. [P-KN]

Lack of the capacity of healthcare system for uptake of medicines

Precision medicine and gene therapies pose an even greater challenge for payers, as many medicines in this category are expected to be quite expensive. Another challenge for payers is the rising cost of diagnostic testing. Diagnostic testing had minimal utility compared to treatment when drugs were used to treat all individuals with a disease. However, while precision medicine diagnostic testing can help pick which individuals will benefit from treatment, it can drastically limit the number of people who use a medicine.

Another trend I see is kind of things moving towards a more precision medicine, personalized medicine type of route, where you’re narrowing down more and more the target population for your treatments, particularly in cancer. So does the health care system have the facilities in place to adequately identify those patients, through genomic testing. For example, if you’re looking at genetic markers, you know is there routine genomic testing and analysis being done in the care pathway. That would allow those patients to be identified early and the appropriate treatments be selected. So, you’re gaining in efficacy by narrowing down and
targeting more and more individually. But you’re also reducing your total revenue, revenue pool and so commercially that’s a challenge. [P-FF]

Gene therapies are another example you know there is high-cost treatments that are highly individualized, but you know vastly more beneficial. How do you accommodate those within the current system. I think it’s challenging, so there are going to need to be reforms made and there are going to need to make changes to the underlying kind of processes and structures to accommodate these things, which would require really close collaboration between the industry and with various external stakeholders as well. [P-FF]

After the medicines are licenced and have completed the HTA evaluation process, there are delays and challenges in the uptake of medicines at the local level. While companies tend to focus on the licencing and HTA evaluation of medicines, the challenges for adoption at the local level are not handled with the same level of attention, slowing the uptake of the product.

I think the biggest challenge is to is to bridge that adoption gap. You know because new medicines take a long time to get through HTA. But it also takes a long time for GPs to write the prescriptions. And we focus as an industry continually at the HTA and understandably because the product can’t be really used until it’s got NICE approval. But actually, the adoption very often slows the growth of the product.... There is a time lag between HTA and GPs writing a prescription and sometimes that can be like years. [P-PM]

The lack of well-defined clinical pathways for new treatments is reported to be a challenge to access to medicines. Pharmaceutical companies are expected to take the lead and contribute more to defining these clinical pathways by collaborating with other stakeholders.

So, there’s a lot of times where clinicians and the evidence don’t really establish what treatments you should take, in what order, and that’s both evidence problem and also a decision-making problem. It’s a responsibility of pharma to provide evidence that is suitable for defining a pathway. Because it’s not really a regulatory requirement, HTA bodies don’t necessarily take it up either. So HTA bodies do make different decisions than regulatory bodies do and do consider more factors. But they can’t decide to consider things outside of the evidence that’s available. So, if the evidence is designed for a certain decision-making rubric, then they’ll make a decision inside that rubric. So, there’s kind of responsibility all along because you need companies to define evidence that is actually good for clinical practice. And you need regulators and HTA bodies to try to do the same thing. [P-MR]
Implementing HTA recommendations is difficult, especially for types of medicines, where hospitals must establish infrastructure or services to administer new medicines, such as intravenous administration.

Implementation is another challenge. Again, it depends on therapy if you are talking about oral therapy that the patient can just take it home then that's not so difficult to implement. Whereas if you are, as I said, looking at a drug that needs specialist services to administer and you might need to set up specialist centres, then there’s always going to be some sort of delay and challenges to getting that therapy implemented. [P-SDS]

According to the participant, if there is still uncertainty in the data and more evidence or data is required, there is an option for cancer medicines as those were funded with the cancer drug fund while waiting for more data to become available. However, non-cancer medicines with gaps in data were not able to get CDF-type funding, which is now expected to be addressed through a new arrangement called the Innovative Medicines Fund.

I think the next one up largely was I guess a hurdle for non-cancer products and we've kind of seen that. There's been positive move with the Innovative Medicines Fund. This would allow them access while they collected more data. Non cancer drugs were disadvantaged if they received or if there was level of uncertainty that the committees were not comfortable with. They would just issue a negative guidance and that would be it. Whereas there is the opportunity to come if it’s within the realms of cost effectiveness that you can go ahead and collect that data. And then go back up after you have it. [P-CD]

Market access decisions are global.

In pharmaceutical companies, market access decisions require cross-functional team input at both the global and country levels, but key decisions to file or not file are made at the above-country level.

I think that sometimes it is not up to the country where they submit or not. Sometimes it is from your worldwide, global counterparts. Whether they let you submit or not. I think the amount of control we have at the country level is very small compared to the people up at the top. [P-SH]

Non-uniformity in decision making
Qualitative data highlight non-uniformity in decision-making as a challenge. While this lack of consistency in decision-making is more prominent for HTA bodies, it also applies to challenges in decision-making at other stakeholder.

*I guess the biggest challenge when you ask about the UK as a whole, non-uniformity in the decision making is one of the things as well. [P-SR]*

**The UK as the centre of innovation and access**

Qualitative data suggest that to establish the UK as the centre of innovation and access, more needs to be done not only for speciality medicines but for wider categories of medicines. Additionally, not only pharmaceutical companies but other stakeholders should be encouraged to support this goal to establish the UK as the centre of innovation and success.

*I guess with the UK, if they wanted to be at the centre of innovation and access. I think more needs to be done in that regard, e.g., mechanisms like conditional approvals, I only see a handful of conditional approval, and that’s mainly in the HST sort of area. Highly specialized, but how about other areas as well, in which other patients can get benefit while the data is collected. So, I think more needs to be done in terms of how they can facilitate data collection, but not just rely on pharmaceutical company, have a partnership approach. And I think having a partnership approach would really benefit. I don’t see that at the moment. So, we’ll see how that pans out in the next five years. [P-SR]*

*If market access delay is a global issue, they have to find incentives to be here if they have to have separate trials why to choose UK. [P-VS]*

**Quality of clinical trials**

Qualitative data suggest that the quality of the trials and trial data, as well as having the right endpoints to meet the needs of both regulatory and HTA submissions, is challenging.

*The biggest challenge is undoubtedly the quality of the trials and the trial data and having the right endpoints measured. [P-NP]*
Digital Healthcare

Qualitative data suggest that digital technology has a very important role to play in improving many facets of medical care, including patients’ access to a variety of drugs. While all sectors, including healthcare, are preparing for this digital shift, the majority of companies appear not to be ready. Therefore, to maximise the use of digital technology, pharmaceuticals must take the lead and collaborate with other stakeholders, including the NHS, not only to provide treatments but also managing the treatment pathway.

*We are slowly moving towards a world where you know health care will be largely sort of digital and it will be based at home rather than in hospitals, and I think you know any sort of new treatments that come out, the ones that the NHS is going to fund, and support are those that you know either enable patient care at outpatients or enable patients to manage themselves at home.* [P-NP]

*If that digital shift happens, there'll be a much bigger expectation on companies to be able to facilitate the remote monitoring of patients on their drugs as well, so that you know building apps or whatever that kind of you know record how you're feeling so that it's easier to sort of risk assess patients. I think that's where we're going to shift care out of hospital but making sure it's sort of facilitated by which kind of digital support and risk stratification which patients are likely to do well or not. I think industry aren't kind of anywhere near that yet really. I think the few companies sort of see it and get it. There's more expectation that pharma contributes more to managing the pathway rather than just simply just providing a treatment and then leaving it to the NHS to work out how to maximize its use really.* [P-NP]

While reporting the results of qualitative interviews in this chapter, we have adhered to the first-person perspective (Watts 2014b), which means prioritising the participants' perspectives, focussing on interpreting the extracts, and presenting findings without judgement or contradiction.

In the next chapter, we will stay committed to the third-person perspective (Watts 2014b) to discuss the results and findings of both the document analysis (Chapter 04) and qualitative
interviews (Chapter 05) in the context of the wider literature and research objectives. This will help us maximise the impact of our findings relative to that literature.
Chapter 6: General Discussions, Study limitation, future work, Overall Conclusions, and recommendations

This chapter discusses the entire research programme in terms of the outcomes of study and is provided according to the stated objectives and research questions indicated in the previous chapter (Chapter 1).

Sections include:

- Discussion of the outcomes of the research
- Study Limitations
- Overall Conclusions
- Future research

6.1 Discussion of the outcomes of the research

The results and findings of both the document analysis study and the qualitative interviews study are discussed in this final chapter in the context of the broader literature. The findings are discussed in light of the research objectives. Where possible, the findings of both document analysis and qualitative interviews are integrated to facilitate a better understanding of the results. This integration of data was done by condensing the findings from different methods, comparing and contrasting the quantitative and qualitative results where needed, and just talking about how their conclusions could be expanded. It also included information on the results of the individual data assessments, as well as the results of the qualitative and quantitative results integration.
Since the findings of the systematic review have already been discussed in detail in Chapter 2, they are not discussed in detail here. However, references to the findings of the systematic review are made where appropriate.

The overall aim of this thesis was to evaluate the access to medicine situation in the UK. This research accomplished this goal by establishing the objectives listed below to investigate this topic. It is explained how the research objectives were achieved throughout the thesis, and how the major findings add to the previous work in the field.

6.1.1 Objective 1: Systematic review of literature on access to medicines in the UK context

Several studies (Cylus and Papanicolas 2015) (Ragupathy et al. 2012) (Takayama and Narukawa 2017) (Ferrario 2018) have looked at various aspects of this topic, ie access to medicines in the United Kingdom. Although some anecdotal evidence was available, a thorough and detailed review of the literature on access to medicines within the UK was lacking, and a systematic review of the literature was needed to fill this gap. As a result, in this PhD research, as a first step, a systematic review has been carried out in this context.

The objective of a systematic review of the literature was to critically review the original research papers and explore the topic in detail. The systematic review included research papers on medicine access, medicine availability, medicine funding, HTA, and medicine legislation. In addition, this review identifies gaps in the available literature and makes recommendations for further research.

Our systematic review showed that access to medicines is different in different countries and for different types of medicines. Access varies because of many things, including differences in health technology assessment, reimbursement, and pricing processes, agency
mandates, characteristics, and recommendation-making processes, stakeholder and societal preferences, differences in the evidence needed to support reimbursement, how submitted evidence is interpreted, and not following reimbursement recommendations (Abbas et al 2019).

Health technology assessment (HTA) has become a key part of recommending prices and insurance coverage, so it is now seen as a closer rather than farther determinant of access. It is important to look at HTA recommendations in terms of how they affect patient access. This review has shown that there needs to be more research into how people in different countries in the United Kingdom get access to medicines (Abbas et al 2019).

The objectives of the research in this thesis are derived from this systematic review of the literature performed and published by the researcher (Abbas et al. 2019). Chapter 2 of the thesis gives a full account of this systematic review of the literature, including methods, results, discussion, and conclusion.

6.1.2 Objective 2: Gap between licensing and health technology assessment recommendations on treatment availability for new innovative medicines in the UK

In Study 1, a document analysis (Chapter 04) of publicly available Health Technology Assessment (HTA) decisions for new innovative medicines in the UK showed that for the EMA medicines licenced in 2017, only a small number of HTA recommendations were aligned with the "licenced indication." The results of document analysis indicated that out of 56 licenced medicines, only a few were found to receive HTA recommendations without any restrictions (Northern Ireland: 21%, Scotland: 22%, Wales: 15%, England: 15%). These findings were also in line with the results of a study conducted by Mycka et al., 2019.
Additionally, this gap between licencing and HTA recommendations was found to vary across different categories of medicines.

While the interview participants in qualitative study 02 (Chapter 05) acknowledged the gap between licencing and health technology assessment recommendations, the qualitative data reveals multiple interrelated factors that impact this gap. Qualitative data also identifies the factors that will have an impact on this gap in the near future, both positively and negatively. It also includes suggestions to reduce this gap between licencing and reimbursement.

Qualitative study data suggest that regulators, HTA bodies, payers, pharmaceutical companies, and patients think differently and have different needs. HTA bodies and payers focus on a broader range of criteria including economic evidence, cost effectiveness, and budget impact, while regulators focus on clinical evidence. That’s the reason we mostly observe a restricted reimbursement recommendation compared to the broader regulatory recommendation. This was also noted in the document analysis (Study 01) of licencing and HTA decisions for 56 innovative medicines. The figure below, taken from the report, clearly shows the disparity in the needs of key stakeholders, that is, the pharmaceutical industry, regulators, payers/health economics bodies and patients (Deloitte 2019b).
All stakeholders must understand this difference in thinking and the differences in needs and priorities and should collaborate to reduce the gap between licencing and reimbursement, which will consequently improve access to medicines.

**Factors likely to increase the gap between licencing and reimbursement of medicines**

*Trends in complex high-tech medicines and limited data sets*

Health technology assessment (HTA) bodies find it difficult to assign an adequate value to high-tech complex medicines (e.g., gene and cell-based therapies) with a limited data set. This implies that these technologies will be unable to successfully navigate the HTA procedure, resulting in a widening of the gap between licencing and reimbursement of medicines. European HTA groups find similar challenges for high-tech complex medicines,
which are primarily due to the scarcity of data rather than the technology's complexity (Deloitte 2019b).

**Limited Budget**

As reported in qualitative data, the government has to reimburse the medicines within the available budget, which is always limited. Every year, NHS England has a certain budget for reimbursing medicines, so by restricting the population, this is saving money for the system. It will be more flexible to cover the broader population as per the licence if there is a the budget available, but if budget is not enough, HTA bodies and payers have to find a way to restrict the population, which results in optimised HTA recommendations.

**HTA bodies/Payers' long-term data requirements**

Short-duration trials save money and get drugs to the market faster. Payer reluctance to adopt new treatments may be attributed to a lack of long-term evidence, which time will solve. Manufacturers should plan for pivotal trial extension analyses and a publication plan. Long-term data communication is especially crucial for new cell-based and gene therapies, where payers pay a considerable cost up front in hopes of savings afterwards due to response durability (Schafer 2018).

**Poor uptake of medicines**

There used to be just three hurdles to overcome for proving the worth of a pharmaceutical product: efficacy, quality, and safety—the focus of regulatory authorities. In this decade, pharmaceutical companies have been used to dealing with a fourth barrier: the need to demonstrate value. As health system decision-makers began to demand not only regulatory-focused thinking but also economic and humanistic considerations, market access and
health economics and outcomes research teams emerged to take this fourth hurdle into account. But four hurdles are no longer adequate to summarise the challenges market access teams are facing today. Even after HTA’s recommendation for the use of a new treatment, it has to go through various steps before it is actually used by patients. For example, after the NICE HTA recommendation, it has to go through subsequent negotiations with NHS England for price. Before clinicians start prescribing, they need to learn about new drugs; new treatments need to be incorporated into the clinical guidelines; and clinicians may need additional training to become confident in prescribing them safely (Daoud 2021).

**Drug Development Decisions Approach**

According to a qualitative study of participants in the pharmaceutical industry, development decisions are made at the global level with little input from country-level organizations. Decisions are based on thinking about the science and regulatory sides, but not necessarily the reimbursement side. As a result, pivotal studies to support development programmes are more aligned to address regulatory requirements.

**Figure 9: Factors likely to increase gap between licensing and reimbursement of medicines.**
Factors likely to decrease the gap between licensing and reimbursement of medicines.

Focus on more specific and targeted therapies

The emphasis on targeted therapies and precision medicines has brought numerous benefits to the entire research and development chain, including increased regulatory approval and more certain drug adoption (Danner et al.2017). One of the key outcomes is a reduction in the gap between licencing and reimbursement of medicines, as we might expect the HTA recommendation to match the regulatory license.

Interim funding in England, Wales & NI (CDF & IMF)

The cancer drug fund is a key part of controlled access in England. It gives patients access to promising treatments at lower prices while NICE waits for more information (Lee, et al.2021).
In June 2022, England started a new fund called the Innovative Medicine Fund (IMF), which is similar to the CDF. The IMF will help people in England who don't have cancer get more cutting-edge medicines faster. Scotland already has a similar fund for new treatments called the New Medicines Fund. Wales has a New Treatments Fund that helps pay for expensive drugs that NICE says are worth money (Roberts 2022).

In September 2018, the Northern Ireland Department of Health outlined mechanisms to guarantee NI patients had equal access to cancer and other therapies approved under the CDF in England (Department of Health 2018b).

The Innovative Medicines Fund (IMF) is modelled after England's Cancer Drugs Fund (CDF), which provides access to promising new cancer medicines through controlled access agreements and interim support for all newly recommended cancer drugs. This method has
been successful in oncology, but it was considered that it may not work for novel non-oncology medicines. The IMF programme limits data collection within a controlled access agreement to five years, which may not allow for robust data to resolve uncertainties, especially for cell and gene therapies with long-term benefit realisation. Small patient populations make randomised controlled trials with acceptable comparators for uncommon disease treatments difficult (Lindup 2022).

*New processes e.g The Innovative Licensing and Access Pathway (ILAP)*

The ILAP was launched on January 1, 2021, to help commercial and non-commercial product manufacturers. The pathway created a single, integrated platform for collaborative consultation with regulatory and reimbursement bodies. It was the first time the MHRA, NICE, the Scottish Medicines Consortium (SMC), and the All Wales Therapeutics and Toxicology Centre (AWTTC) met with supporting partners to streamline the "bench to bedside" pathway (Baig 2022). The work done to support ILAP products should let companies come up with and submit well-evidenced value propositions. This way, products that get a marketing authorization from the MHRA have a good chance of also being recommended by NICE guidance (Crabb and Boysen 2021).

*NICE methods review (Change in end-of-life criteria to severity criteria)*

After the UK’s departure from the European Union, the evolution of the regulatory and HTA environments will indeed be crucial success factors in attracting future investment from the global life sciences industry. To that end, it is crucial that NICE’s methods be updated so that they can accurately and thoroughly evaluate the value of medicines currently in development within the pharmaceutical industry. The continued prominence of NICE and
the NHS as global leaders in healthcare delivery depends on their ability to adapt their appraisal methods in the light of new evidence and shifting clinical priorities (Catchpole and Barrett 2020).

Recent modifications in NICE methodologies for new evaluations could enable patients’ faster access to promising new therapies by giving more flexibility over value-for-money decisions and a broader evidence basis. Key changes included in the recent update are described below (Gillian Leng 2022).

Adding weight to health benefits in the most severe illnesses to provide more fair access to treatment, not just end-of-life treatment, and adopting new approaches to evidence, e.g., how to use real-world evidence, gives the independent committees of NICE more freedom when there is not much evidence. Sometimes it might be hard to do research on children’s problems, rare diseases, or new or advanced treatments. The changes will make it easier for NICE’s committee to weigh the unknowns and manage the risks to patients and the NHS without getting in the way of good changes. This includes adopting a clearer vision, set a set of principles, and routing criteria for NICE’s Highly Specialised Technologies (HST) programme. This would make routing topics to the programme faster, more predictable, and clearer. It would also help NICE achieve its goal of giving everyone in the NHS equal access to specialised medicines. Previous discussions with NHS England, NHS Improvement, and businesses about commercial and managed access options that allow NHS patients to receive treatment while more data is gathered When NICE committees might suggest managed access, it will be easier to see (Leng 2022).
To close the gap between medicine licencing and reimbursement, qualitative study propose encouraging access primarily through interim arrangements followed by a more formal HTA, exploring and addressing the challenges of uptake at the local level, and allowing access at the point of licence and imposing restrictions later, as Germany does.

6.1.3 Objective 3: Timelines from licencing to reimbursement of medicines

Studying the time lag between licencing and reimbursement provides important information about the access to medicines situation in any country. While study 01, that is, document analysis, focused on the time lag between licencing and HTA recommendation, interview participants in study 02 were asked questions about all related time lags between licencing and reimbursement. The first-time lag was from licencing to HTA application submissions. The second time lag was from HTA application submission to HTA recommendation. The third time lag was from HTA recommendation to reimbursement.

Document analysis in Study 01 has provided information solely on the actual time lag, i.e., a quantitative piece of information. However, the qualitative study 02 has provided information about the contributory factors and trends of these time lags. The European Commission Transparency Directive 89/105/EEC mandates national pricing and reimbursement recommendations within 3 months after licencing approval.
(Flostrand et al., 2014). However, in document analysis study 01, the time from licence approval to reimbursement recommendation varies (2 months to 30 months) across the UK countries. In fact, in the majority of cases, it is longer than 3 months.

**Figure 11: Key Milestones from Development to Access to Medicines**

Adapted from source (EFPIA 2020a)

**Time Lag from Licensing to HTA application submissions**

HTA bodies must make timely drug reimbursement recommendations to ensure patient access. HTA timings are being monitored by researchers as an indicator of drug availability (Wang et al., 2019; Zamora et al., 2019). However, many studies have only looked at the entire period from regulatory approval to HTA recommendation because HTA submission dates are not publicly available (Wang et al., 2020a).

Once a drug obtains an MA, reimbursement could still be delayed. Some countries wait for the formal EMA decision and/or reimbursement decisions in other countries before starting their own. Even so, the length of P&R varies by country (EFPIA 2020b).
The EU Transparency Directive (Directive 89/105/EEC) (Community 1988) gives member states 180 days to issue P&R decisions; however, this may be substantially longer due to clock stoppage or lack of conformity. In various markets, some medicines get quick access after marketing approval. In Germany, the usual method gives manufacturers a limited term of free pricing that allows access to an EMA-approved pharmaceutical nearly from day one, avoiding the delay caused by HTA review and pricing negotiations. In many markets, the pricing & reimbursement procedure doesn't start automatically; the pharmaceutical company must submit an application (EFPIA 2020b).

This depends on the rules: In some countries, dossiers can be submitted or assessed before marketing authorization, but in others, a positive opinion from the EMA Committee for Medicinal Products for Human Use (CHMP) (European Medicines Agency n.D.) a formal decision from the European Commission, or publication in the Official Journal of the EU is required. In certain circumstances, countries wait for decisions from others, and in others, national processes cannot begin until a cohort of other countries finalises its judgment (EFPIA 2020b).

Study 02 qualitative data also shows that in England the process can start significantly before the marketing authorization, whereas in Scotland there is a delay in submission even after a positive opinion from the regulator. The UK PharmaScan (Anon n.d.) horizon scanning process has helped speed up HTA submission planning.

According to the document analysis study, absences, or long delays in HTA submissions have been observed. This absence or long delay of HTA submission was further investigated in Study 02 through qualitative interviews. According to qualitative data, lack of mature data,
challenging HTA bodies' requirements and clinical trials that did not perform well, data collection agreements, commercial viability/size of market, treatments being not cost-effective, resource constraints were recorded as possible reasons for delay or absence of HTA submission. Deprioritisation of medicine in the UK compared to other EU countries, pricing impact for medicine that is targeted for multiple indications, non-selection of treatments for NICE appraisal, and drug discovery that is kind of incremental were also recorded as potential causes. Additionally, political pressure for earlier access compared to other countries and the UK’s status as a reference country may also impact the decision to file HTA applications.

According to Study 02 qualitative data, the UK is among the first few countries in Europe where HTA filing is prioritized. This prioritisation is also due to the influence of NICE on reimbursement decisions in various countries. In countries inside the UK, a staggered approach is followed, i.e., filing to NICE comes first and then to SMC, and it is also driven by company objectives, the size of the market in the individual country, and the level of flexibility to start the HTA process sooner.

Sometimes HTA submissions to NICE and SMC are handled in parallel. In some cases, HTA submissions to SMC are earlier than NICE submissions because companies foresee challenges with NICE submissions. AWMSG in Wales usually follows NICE recommendations. AWMSG submissions can be made either in the absence of NICE submissions (e.g., HIV drugs are not appraised by NICE) or if long delays in filing to NICE are anticipated. Companies also consider filing with AWMSG in the case of a negative NICE recommendation. HTA
assessment is not performed in Northern Ireland. They refer mostly to NICE recommendations and to SMC recommendations in some cases.

**Time Lag from HTA Application Submission to HTA recommendation**

This time lag starts as soon as the HTA process gets started and lasts until the process is finished and a recommendation has been made. The timelines for the HTA procedure are well established. (Anderson, Drummond, et al. 2022a) As noted in the qualitative data, these timelines could go up to 12–18 months or even up to 2 years, depending on the number of committee meetings needed to complete the evaluation process.

The HTA process at the Scottish Medicines Consortium (SMC) is relatively faster. The usual assessment timeline is 18 weeks, i.e., from the scheduling of a submission to the publication of advice. A longer timeline, e.g., 22–26 weeks, is required for submissions for end-of-life orphan medicines, medicines with a complex patient access scheme (PAS), and occasionally for complex submissions, e.g., ones that include multiple clinical studies (SMC 2022)(Anderson, Drummond, et al. 2022a). Although Wales follows NICE's recommendation, in the cases where AWMSG performs its own appraisal, the timeline for appraisals is the shortest, i.e., 20–21 weeks (Anderson et al. 2022a).

**Time Lag from HTA recommendation to Reimbursement**

Local commissioning bodies in England and health boards and health trusts in Wales and Northern Ireland have a legal obligation to make new medications approved by NICE available to patients in their jurisdictions. Similarly, it is a legal requirement that relevant bodies in Wales provide access to new medicines approved by AWMSG. However, in
Scotland, SMC decisions are not binding and are only considered advisory (Anderson et al. 2022a). In England, it is the responsibility of local commissioning bodies to make funding available for a drug or treatment recommended by NICE no later than 90 calendar days (30 calendar days for EAMS products or products appraised via the Fast Track Appraisal process), unless otherwise specified in the guidance (NICE 2022). In Wales, health boards and trusts have a 60-day deadline to make a newly recommended medicine available for prescribing (AWMSG 2022). As noted in the qualitative data, SMC recommendations are considered advisory, and there are no explicit timelines for implementation. There is a concern arising from the fact that local health boards did not always follow the SMC recommendations (Wilsdon et al. 2014).

**Trend for the time lag between licencing and reimbursement**

According to the qualitative data, the majority of the participants were of the view that the time lag between licencing and reimbursement would decrease. NICE methods review, earlier HTA submissions, interim access agreements, ILAP, EAMS, and the UK government’s aspiration to lead the life sciences industry were considered to contribute to a decrease in the time lag between licencing and reimbursement.

Some participants were of the opinion that there would be negative impact on this time lag. High volume of HTA submissions, complex techniques and technologies for development, NICE efforts to shorten evaluation timelines, expedited regulatory processes, and lengthy negotiations with NICE and the NHS were all cited as reasons to support the aforementioned position.
Qualitative study participants' suggestions to reduce the time lag between licencing and reimbursement are also listed below.

Table 11: Suggestions to reduce the time lag between licensing and reimbursement

<table>
<thead>
<tr>
<th>Early involvement through ILAP, EAMS (early scientific advice) and consultation with relevant stakeholders through processes such as the Office of Market Access and Consulting Group.</th>
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<tbody>
<tr>
<td>Better use of opportunities to expedite access, e.g., Project Orbis</td>
</tr>
<tr>
<td>Project Orbis is a collaboration between US, Canadian, Australian, and UK drug regulatory authorities to accelerate cancer treatment approvals. The UK's inclusion in Project Orbis allows for a coordinated submission approach across several markets and early patient access to less mature data. This must be evaluated against reimbursement expectations; delays in NICE submissions or data collection agreements through the Cancer Drugs Fund may be needed to demonstrate cost effectiveness (Kim, Ceccarelli, and Lu 2021).</td>
</tr>
<tr>
<td>Examples of Products approved through Project Orbis</td>
</tr>
<tr>
<td>The first one was AstraZeneca's Tagrisso for lung cancer, which received an authorization from the Medicines and Healthcare Products Regulatory Agency (MHRA) under Project Orbis in only four months, in May 2021. Guidance from NICE on Tagrisso (osimertinib) for this type of lung cancer is not due until September 2021 at the earliest. But under Orbis, NICE, in agreement with NHS England, enabled early</td>
</tr>
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</table>
access to ensure patients had the chance to benefit from the new treatment option (Staines 2021).

The second is Amgen’s drug marketed as Lumakras for non-small cell lung cancer (NSCLC), which received UK MHRA approval in September 2021. NHS England, NICE and Amgen reached an agreement to allow early access to Sotorasib for eligible lung cancer patients in England on a budget-neutral basis, while NICE completes its ongoing appraisal. Patients in the UK were the first in Europe to receive the medicine (Taylor 2021).

The examples above are excellent examples of accelerating access to medicines by reducing the time from licence to reimbursement to zero.

Advance planning of new treatment launches through data generation and landscape analysis Identify gaps in data packages. Make a map of all possible routes. Identify the candidates who could take advantage of accelerated routes.

Discussions with NHS in advance for service readiness

Early communications/discussions particularly with NICE before committee meetings and even before submissions

More clarity around related processes, evidence requirements and timelines

Use of Innovative access agreements
6.1.4 Objective 4: Differences/variability in health technology assessment recommendation across countries in UK.

The document analysis in study 01 shows the variability in the HTA recommendations across countries in UK, which is in line with the results of the studies conducted by Mycka et al., 2019, McKendrick et al., 2017, Blázquez, et al.. However, the variability across countries in the UK is not as large as was observed for the countries in the EU.

In document analysis study 01, HTA assessment recommendations were also reviewed for different categories of medicines, including orphan medicines and non-orphan medicines, oncology medicines and non-oncology medicines, and non-expedited/standard pathways and expedited licencing approval pathways.

Our document analysis study results showed that orphan medicines in the UK received more HTA recommendations than non-orphan medicines, and the majority of the HTA recommendations were without restrictions. This also predicts better availability of orphan medicines.

This result is not consistent with the earlier findings, which state that the rate of availability of orphan medicines compared to non-orphan medicines is lower across the EU countries (EFPIA 2019). The results of the document analysis study also showed that oncology medicines in the UK received more HTA recommendations than non-oncology medicines, and the majority of the HTA recommendations were without restrictions. This predicts better availability of oncology medicines. These results are consistent with the earlier
finding, which states that the availability rate of oncology medicines is higher than that of non-oncology medicines.

In the document analysis study, only a small number of medicines were licenced via a non-standard (conditional or exceptional circumstances) approval pathway. Hence, it was difficult to interpret the results as the study included a limited number of medicines licenced via a non-standard pathway. However, variability in HTA recommendations was observed across the UK countries.

Although the results of the document analysis study showed the state of this variability in HTA recommendations across countries in the UK, the qualitative study findings also acknowledge this variability and explore it further by discussing the key drivers that play the part in this variability. Study 02 qualitative data also discusses the trend for variability and makes suggestions to decrease this variability in HTA recommendations and reimbursement across countries in the UK.

The qualitative data highlight the following factors that could potentially result in variability in HTA recommendations and reimbursement across countries in the UK. Access to medicines in the UK varies from country to country due to differences in healthcare systems, policies, political factors, prevalence of disease and standard of care.

After devolution, the policies of the four UK countries are so different that it is no longer possible to have a UK-wide national health service (NHS). The devolved governments have made different decisions about how to support the publicly funded health system, how it is organised and run, and what benefits are given to their citizens. In Scotland, general prescriptions and personal care are free, but not in England (Bevan et al. 2014).
Here’s a recent example of how the National Institute for Health and Care Excellence (NICE) surprised and disappointed patients with metastatic castration-resistant prostate cancer by recommending against using Olaparib on the NHS in a draft guidance document published on January 5, 2022. But in October 2021, the Scottish Medicines Consortium said that the drug should be used for the same purpose in Scotland. This variation in the decision may make it harder for people in England, Wales, and Northern Ireland to access this medicine (The Lancet Oncology 2022).

Since NICE, SMC, and AWMSG are independent HTA bodies, they have different remits and scopes. Each HTA body has its own resources, budgets, and capacity. Generally, HTA agencies will evaluate the therapeutic value and cost-effectiveness of a health technology. The scope and methodologies used to conduct HTA can, however, vary greatly among agencies. Political, social, and financial differences cause HTA bodies to have different philosophies and methods (Allen et al. 2013).

Each HTA body has its own evaluation processes and methodology. NICE has a more stringent and clearly defined ICER threshold and shows flexibility in the cost per QALY threshold for end-of-life and highly specialised treatments. SMC does not have published thresholds, but uses six modifiers along with its consideration of the incremental cost per QALY (Anderson et al. 2022b).

According to our qualitative study participants, NICE HTA outcomes are relatively inconsistent compared to SMC. The inconsistency in NICE HTA outcomes is attributed to differences in the working styles of NICE’s various committees and evidence review groups. This inconsistency does bring variability in HTA recommendations, not only between NICE
and other HTA bodies but also within the NICE recommendations across different products. SMC is recommending more therapies. NICE decisions are considered more restrictive than SMC.

Moreover, HTA evaluation times for NICE are longer than those for SMC. There are different interim funding arrangements, e.g., CDF and IMF, for patients in England, but arrangements in Scotland and Wales are different. It was noted that SMC doesn't have a way of dealing with additional data collection. While all UK HTA bodies measure the cost-effectiveness of new treatments, SMC was considered to put more emphasis on the cost-effectiveness of the drug. The SMC Patient and Clinician Engagement (PACE) process gives patient groups and clinicians a stronger voice in SMC decision-making.

According to qualitative study participants, the HTA process is easier and faster in Scotland but difficult in England. Historically, it was harder to get through SMC compared to NICE. Presently, it is harder to get through NICE than SMC. In some cases, pharmaceutical companies’ poor understanding of different healthcare systems due to a lack of resources, particularly skilled human resources, HTA bodies’ requirements, and related country-specific factors. These can also contribute to variability in access to medicines.

According to participants in our qualitative study, variability in HTA recommendations is usually considered negative as it causes inequality in access to medicines, but variability has its pros as well, pros in the sense that if the HTA recommendation of an HTA body, e.g., the NICE recommendation, is negative, then at least patients in Scotland could have access if the SMC recommendation is positive.
As observed in the document analysis study, variability is not the same across different categories of treatments and tends to exist more for rare disease treatments. Variability in access to medicines across the UK is not only due to variability in HTA recommendations, but also because of variability in uptake of medicines at the regional or local level due to differences in infrastructure for implementation. There is further discussion around medicine uptake under objective 05.

Qualitative study participants have mixed opinions about the trend of a decrease or increase in the variability of HTA recommendation and reimbursement in countries in the UK. According to some participants, variability is likely to increase as NICE's revised methods, if not implemented well, this could also result in more restrictive recommendations. Other factors considered to contribute to variability were inconsistencies in the results of NICE HTA due to different evidence review groups (ERGs) and committees, the opportunity for abbreviated submissions in SMC but not in NICE, and patients' greater engagement in the SMC process than in the NICE process.

According to the qualitative study, variability is likely to decrease due to the introduction of various initiatives such as ILAP, the UK government's priority to fund health services in all regions, revised NICE methods if implemented well, project Orbis, aiming to deliver faster patient access to innovative oncology medicines (Lythgoe and Sullivan 2022), increased interaction between HTA bodies, standardisation of formularies, and standardisation of guidelines and treatment policies.

To decrease the variability in HTA recommendations and reimbursement across countries in the UK, the qualitative study participants suggested more collaboration among HTA bodies.
throughout the UK, early engagement, use of RWE data, more flexibility in pricing for all regions, better sequencing of HTA submissions, and continuing to have independent HTA bodies with uniformity in the evaluation process.

6.1.5 Objective 5: Medicine uptake post-licensing and/or health technology assessment recommendation

**Medicine uptake after HTA recommendation**

On average, it takes 17 years for a clinical practise to adopt an intervention supported by scientific evidence (Morris et al. 2011). Medicines are the most widely used therapeutic intervention in healthcare, and they also account for a disproportionate share of the industry's overall budget (Ewbank et al. 2018). Improvements in patient health outcomes and healthcare efficiency, as well as the country's international competitiveness in the life sciences industry, might be slowed by insufficient uptake of cost-effective and new medicines (Ewbank et al. 2018) (Office for Life Sciences and Welcome Trust. 2016). For example, compared with health care systems in Australia, Canada or France, the United Kingdom's (UK) uptake of nationally prescribed new medicines is generally lower than in other comparable nations (Henley and Blackwood 2019).

Although most of the challenges related to access to medicine centres on delays in marketing authorization, price negotiation, and reimbursement regulations, issues after these traditional ‘market access’ phases can dramatically affect the time it takes for patients to get proper proper treatment (EFPIA 2020a). Access to 13 recently introduced medicines ranged from 61% to 0.3% in 16 countries 12 months following reimbursement (EFPIA 2020b) .
The qualitative data in my study suggest that positive HTA recommendations do not necessarily result in positive reimbursement decisions, as these decisions are made at the regional level. Historically, negotiations with payers began after the HTA recommendation, but now there is a drive to start this process early.

Qualitative data also suggests a slow and lower uptake of medicines following HTA recommendations at a UK-wide level. For approximately 75 novel medicines recommended by NICE and introduced between 2013 and 2019, UK per capita use in the first three years after reimbursement was around 64% of the average in 15 comparative countries (Mp and Bethell 2021). Despite having the lowest pricing, numerous drugs can't debut in the UK when we launch new medicines, the UK is already left out. Although access and uptake choices are not often made at a UK-wide level, the industry believes there is no notable difference between the UK's four devolved nations in access, uptake, and outcome compared to other key global pharmaceutical markets (The Association of the British Pharmaceutical Industry 2022).

The qualitative study findings suggest that the rate and extent of the uptake depend on the type of medicine, unmet needs, competitive landscape, place of residence (rural or urban), new molecule, or new indications. The degree of agreement between HTA recommendations and reimbursement decisions varies significantly between countries. The size of medicine uptake is determined by constraints at the HTA body level and regional levels.

Qualitative study data suggested more variability in the uptake of medicines in England compared to other regions of the UK. The Information Centre for Health and Social Care's
recent report identified considerable disparities between expected and observed use of NICE-approved drugs (Collins 2020). The literature suggests a number of common themes that influence UK medicine access and uptake compared to other countries. These include health technology assessment, service planning, organisation, direction setting, and clinical culture (Richards 2010) (EFPIA 2020b).

Medicine uptake issues or challenges following positive HTA recommendations as described by qualitative study participants are discussed below in the context of the literature. HTA recommendations and implementation challenges have two main impacts: the first is the delay in access to medicines, and the second is the impact on the breadth of access.

According to the qualitative study, participants’ regional bodies (CCGs and ICSs in England and health boards or other related bodies in other UK countries) have their own budgets and treatment guidelines. Because of limited budgets, regional health bodies or payers can impose further restrictions following HTA body recommendations. In some cases, informal restrictions at the physicians’ prescription level are also reported. Most pharmaceutical availability and delay studies focus on national reimbursement. Decision-making has many layers. In some countries, funding decisions must be made at the national, regional, and hospital levels, delaying patient access to therapies (EFPIA 2020b).

Budget impact thresholds are applied in England but not in Scotland & Wales. NICE adopted the budget impact (BI) test for technology appraisals (TAs) in April 2017, delaying funding for therapies with a budget impact of more than £20 million in 1 of the first 3 years (Tuson et al. 2017).
Additional funding for diagnostic tests or biomarker tests is restricted. However, it is also vital that diagnostics need proper reimbursement. (EFPIA 2020b). Health system performance and infrastructure can affect drug access. A successful healthcare system provides patients with access to high-quality healthcare facilities, diagnostic centres, and healthcare professionals. Clinical pathways should facilitate the optimal use of novel medicines by ensuring timely detection and diagnosis through screening and recognition of risk factors, coverage of appropriate biomarker testing, prompt referral to centres of excellence when necessary, and the absence of financial considerations for prescribers and patients. Access to new medicines may be impacted by a health system's capacity to adapt and incorporate novel therapies (Kamphuis et al. 2021).

Various NHS programmes and academic health research networks strive to speed up the adoption of cost-effective new medicines and technologies. The government initiated an 'accelerated access review' in 2014 to speed up NHS patients' access to innovative medications, equipment, and diagnostics. NHS England formed the Accelerated Access Collaborative (AAC) after the review to speed up the adoption of novel treatments. The government gives financial incentives and support for the chosen pharmaceuticals. (Ben Collins 2020)

According to qualitative study participants, new treatments are not always added to clinical guidelines. The lack of clinical guidelines could cause delays for two reasons. First, horizon scanning might miss a new medicine, which would delay HTA decisions. Second, prescribers might be hesitant to use new medicines because they aren't sure how to use them (EFPIA 2020a).
Qualitative study participants suggest improving the extent and rate of uptake by early engagement with all stakeholders (Payers, physicians & Patients), pharmaceutical companies should understand how treatment will affect overall service. They should also investigate ways to influence treatment guidelines, therapeutic protocols, and entry into formularies.

**Medicine uptake without HTA recommendation/ Negative HTA recommendation**

According to the document analysis study presented in this thesis, the absence of HTA submissions has been observed. This absence of HTA submissions was further investigated through qualitative interviews. According to qualitative data, lack of mature data, challenging HTA body requirements, particularly long-term data, clinical trial trials did not perform well, data collection agreements, commercial viability/size of market, treatment were not cost effective, resource constraints, reprioritization of UK compared to other EU countries were recorded as possible reasons for delays or absence of HTA submissions.

Other reasons given in qualitative data were the effect of prices on medicines that are used for more than one purpose and the fact that treatments were not chosen for NICE appraisal. Political pressure for faster access than other countries and the fact that the UK is a reference country also play a role in whether or not HTA applications are filed. Since finding new medicines is a kind of a step-by-step process, showing small improvements over existing medicines was listed as a possible reason why HTA submissions were late or did not happen at all.

According to the document analysis study presented in this thesis, no HTA submissions have been observed. This absence of HTA submissions was further investigated through
qualitative interviews. According to qualitative data, possible reasons for delays or absence of HTA submissions include a lack of mature data, challenging requirements of HTA bodies, long-term data, clinical trials that did not perform well, data collection agreements, commercial viability/size of the market, treatments that are not cost effective, resource constraints, and prioritisation of the UK compared to other EU countries.

Further reasons reported in qualitative data included the pricing impact of medicines targeted for multiple indications, the nonselection of treatments for NICE appraisal, and the fact that drug discovery is a kind of incremental, i.e., showing trivial improvements over existing products, all of which were recorded as possible reasons for HTA submission delays or absence. Additionally, political pressure for earlier access compared to other countries and the UK’s status as a reference country may also impact affected the decision to file HTA applications.

The assessment gap, or the absence of HTA guidance, might alter local clinical priorities. The assessment gap is one of the unintended consequences of the NICE topic selection process and the well-intentioned statutory funding directive. NHS organisations in England are obliged to make funding available for the treatment of patients whose clinicians recommend treatment in line with NICE appraisals within three months of the appraisal being published (Parliament. House of Commons 2012).

Until recently, many breakthrough new drugs launched each year did not undergo NICE appraisals and may not have benefited from a retrospective multiple technology appraisal or clinical guideline inclusion. These drugs have never been evaluated clinically or economically. When medicine does not meet the selection criteria for appraisal and is
marketed without a positive review and funding directive, certain NHS organisations may feel the absence of guidance is notable and struggle or decline to make funds available to support the uptake of that innovation.

This is called the "assessment gap," and it means that a medicine doesn't get used as much because its clinical and cost-effective merits haven't been evaluated (Parliament. House of Commons 2012). NICE recently changed how it chooses which topics to study, which will increase the number and types of new medicines that are looked at. The following qualitative study data talk about how to access medicine when HTA doesn't recommend it or the absence of HTA recommendations.

**Payers overturn negative recommendations**

Negative recommendations from HTA can be overturned either through a new pricing agreement or data collection agreement. Two rare disease case studies—Orkambi® for cystic fibrosis and Spinraza® for spinal muscular atrophy—illustrate how HTA bodies prevented patients in dire need from accessing new, innovative treatments and then payers intervened and overturned the HTA recommendations. These cases are discussed below and were originally presented in Alexion Pharmaceuticals' report on challenges in preserving access to orphan drugs (A. R. D. Alexion 2021).

**Case Study #1: Cost concerns deny thousands of patients access to the needed treatment**

Ivacaftor/lumacaftor—sold under the brand name Orkambi®—was developed to treat cystic fibrosis, an inherited condition that causes people to produce mucus that is thicker and stickier compared to people without the condition, leading to clogged and damaged critical organs. Cystic fibrosis is a rare genetic disease that affects approximately 100,000 people
around the world, including approximately 10,600 people in the UK. To improve the lives of people living with cystic fibrosis, U.S.-based Vertex Pharmaceuticals developed Orkambi®, which works by targeting the chloride channels in the body that control mucus production.

Orkambi® is specifically effective for patients who have the F508del mutation on both copies of the gene, the most common mutation in people living with cystic fibrosis. Orkambi® was found to reduce hospitalization among cystic fibrosis patients, and when the drug was submitted for consideration to NICE in 2015, the agency concluded that the drug could have clinical benefits for approximately 2,750 cystic fibrosis patients in England.

However, like many orphan drugs in the UK, Orkambi® was not eligible for the HST pathway and instead underwent assessment through the STA pathway, which is not designed to evaluate orphan drugs. In 2016, NICE denied government reimbursement for the drug, saying that the cost of the drug was too high to be a "cost-effective use of NHS resources."

In its assessment, the HTA body further determined that Orkambi®, which would cost about £104,000 per patient, showed "modest" benefits compared to existing treatments. In the NICE announcement, the agency said that it would "only recommend treatments when they are certain, they are clinically effective and represent good value for money," saying they would "welcome" Orkambi® "at a cost-effective price." The debate over the cost-effectiveness of the drug continued for more than three years.

Meanwhile, in comparable countries, including the U.S. and other parts of Europe, Orkambi® has been available as a treatment since 2015. As the wait continued, Orkambi® proved to reduce rates of lung function decline by nearly 50 percent in cystic fibrosis patients. The Cystic Fibrosis Trust further suggested that additional real-world data demonstrating the
long-term benefits of Orkambi® could be collected and distributed to the HTA body to speed up the decision; however, NICE officials said they would only review the data if the price were lowered.

After years of pressure from cystic fibrosis advocates and patients, in 2019, the NHS reached a deal with Vertex where it agreed to appraise Orkambi® and other cystic fibrosis pharmaceuticals if the company submitted its full portfolio for appraisal. ‘The decision [to appraise Orkambi® in the UK] came years after the drug was made available in other countries, and activists maintained that the HTA body’s fixation on cost - and its disregard of additional proven benefits - led to unnecessary suffering and death among cystic fibrosis patients’ (A. R. D. Alexion 2021). The evaluation is set to conclude in 2021, and it will take 18 months to collect data from the real world. However, the decision came years after the drug was made available in other countries, and activists maintained that the HTA body’s fixation on cost—and its disregard of additional proven benefits—led to unnecessary suffering and deaths among cystic fibrosis patients (A. R. D. Alexion 2021).

Case Study #2: A subset of patients miss out on breakthrough therapy due to strict HTA eligibility. Spinraza® (nusinersen), developed by American biotechnology company Biogen, is the company’s first-in-class treatment for spinal muscular atrophy (SMA), a genetically rare disease that affects the central and peripheral nervous systems, as well as voluntary muscle movement. People with spinal muscular atrophy experience severe muscle weakness and waste, making the disease fatal for many children diagnosed with the condition.

About 68 percent of children with spinal muscular atrophy type 1—the most common form of the disease—die before they turn two years old. In multiple clinical studies involving more
than 170 patients, Spinraza® was shown to improve motor function in patients with infantile-onset spinal muscular atrophy compared to patients in the control group.

For instance, a larger percentage of patients (51 percent versus 0 percent) treated with the drug were able to reach motor milestones including standing, walking, and sitting unassisted at ages when those functions are expected to be impossible. Spinraza also reduced patients’ chances of death or permanent ventilation by 47 percent compared to patients in the control group.

In 2016, the FDA approved the drug for spinal muscular atrophy, and it was later given marketing authorization by the European Commission in 2017. However, despite Scotland and other parts of Europe granting approval to the drug, Spinraza® experienced approval delays in England after NICE rejected its proposed price in August 2018, leaving patients in the UK without access to the only available treatment for the devastating and fatal disease. Spinraza®, like many other rare disease drugs, did not qualify for NICE’s HST appraisal pathway used for orphan and ultraorphan drugs and was instead forced to undergo consideration under NICE’s standard STA process.

Through STA, NICE found that the drug’s cost, which was about £450,000 for the first year of treatment and £225,000 for subsequent years, was too high to justify the treatment gains, despite the drug showing a "substantial benefit." In a statement, NICE claimed that it had "significant uncertainties, particularly around long-term benefits," despite new data introduced that year showing that showed infants, teens, and adults exhibited continued improvement in the drug. Similar to the case with Orkambi®, activists pushed for NICE to reconsider its decision, especially as new data continued to show the drug’s effectiveness.
Finally, in 2019, NICE formed a managed access agreement (MAA) with the NHS and Biogen, which allowed Spinraza® to be available to a subset of patients as long as NICE could continue to collect data on the treatment’s efficacy and financial impact.

Even the MAA had limitations: Spinraza® was available to almost all patients with spinal muscular atrophy, with the exception of type 3 patients who had lost their ability to walk. In May 2021, NICE announced that "the review has concluded that it is appropriate to extend the clinical eligibility criteria to allow access to [Spinraza®] for patients with type III spinal muscular atrophy who aren’t able to walk," making the one-of-a-kind treatment available to all. However, it is unknown how many more patients may have benefited from the treatment had it been available in 2018. Overall, the strict criteria for the HST appraisal pathway have limited many orphan drugs from being widely available. Of the 24 STA reviews of orphan drugs conducted by NICE between 2013 and 2017, only 13 percent were recommended for the full population that was made eligible through EC authorization, compared to the full recommendation for 66 percent of non-orphan medicines (A. R. D. Alexion 2021).

**HTA process can be averted in exceptional circumstances**

Our study participants quoted recent examples of COVID-19 vaccines and treatments, where the HTA process was averted for very low-cost medicines as well. Historically, there are some categories of drugs that do not have to go through the HTA process, for example, HIV treatments.

**Patient Access Agreements**
According to a qualitative study, clinical commissioning agreements, value-based agreements, value-based partnerships, national agreements with the NHS rather than NICE, and agreements at the local level are examples of various patient access agreements.

NHS Procurement Partnership with Gilead Science for the first hepatitis C cure (Sovaldi). This historic agreement has the potential to make England the first country in the world to completely eradicate the deadly virus disease (NHS England 2019).

NHS England successfully negotiated deals for a variety of new treatments in 2021, including drugs that may allow toddlers with spinal muscular atrophy to walk. The one-off gene therapy treatment Zolgensma, which has been described as the world’s "most expensive" drug with a list price of £1.79 million, has been successfully given to a few young children through managed access agreements (BBC 2022).

Early subscription-based AMR agreements: Zavicefta and Fetcroja, Pfizer and Shionogi In 2019, the NHS and NICE announced a trial of the innovative "subscription-type" payment model for antimicrobial resistance (AMR). AMR refers to the process by which microorganisms develop defences against antimicrobial drugs, enabling these microorganisms to adapt and become resistant to treatment (Richardson et al. 2022).

Using this kind of "Netflix" payment approach will mean moving the NHS away from paying for individual packs of antimicrobials and, instead, making an annual payment based on the health benefits to patients and the value to the NHS. The proposal of a subscription model served to incentivise companies to invest in this critical area, with the objective of securing a pipeline of future treatment options for NHS patients (Richardson et al. 2022).
As an early phase in pursuing this model, in 2020, the NHS and NICE selected two treatments, Cefiderocol (Fetcroja) manufactured by Shionogi and ceftazidime with avibactam (Zavicetna) manufactured by Pfizer, to move to an innovative health technology evaluation process, followed by the design and rollout of a subscription-based payment model. The details of this model are currently being finalised but will likely be ten-year contracts (Richardson et al., 2022).

According to these contracts, the NHS will pay a fixed annual fee of £10 million for access to cefiderocol (Fetcroja) and avibactam (Zavicetna), regardless of how much is used to treat patients. This flat fee has been calculated based on the value that the therapies offer the health service. Significantly, this Value Based Approach (VBA) is one of the first of its kind globally, underscoring the UK’s innovative leadership in the area and providing critical pharmaceutical industry incentives to invest in AMR therapies (Richardson et al. 2022).

**Interim access arrangement or Interim funding**

NICE now reviews novel cancer medicines using the revised Cancer Drug Fund. NICE plans to assess all newly licensed cancer medicines within 90 days. It now also evaluates uncommon cancer medicines, which is new. Before 2016, NICE did not consider rare cancer medicines (Cancer Research UK 2019).

When NICE approves a medicine, it enters the CDF for 90 days until the decision is verified. Once confirmed, NICE departs CDF. Then it’s routine. It’s now immediately available. Before 2016, this was not true. A "No" from NICE signifies the medicine is ineffective. Or it fails NICE’s value-for-money criterion. So it’s not approved for the NHS or CDF. A CDF recommendation means the medicine shows promise in studies. There is not enough
evidence to say "yes" yet. It could be advised for use within CDF recommendations. There’s more time to gather drug effectiveness data. Reviewers may also take into account NICE’s value for money criterion. NICE decides whether to approve the medicine after two years on CDF (Cancer Research, UK 2019).

Yescarta, a CAR-T therapy for children and teens with a rare form of leukaemia, was licensed in August 2018. The treatment’s full list price was approximately £300,000 per patient, but a commercial deal with NHS England allowed NICE to accept its admission into the Cancer Drugs Fund (Pharmaceutical Technology 2018).

No one outside of England can apply to the Cancer Drugs Fund. You need to qualify for free healthcare from the NHS. A primary care physician (PCP) registration in England is also required. There are variations in how quickly and easily people in Scotland, Wales, and Northern Ireland can get their hands on cutting-edge medications. Scotland even has its very own new medicines fund” for developing and implementing innovative medical treatments. Patients with extremely rare diseases or those who are at the end of their lives can access this fund to help with the cost of their medication (Cancer Research UK 2019).

Orphan diseases afflict less than 1 in 2000 persons; hence, in March 2013, the Rare Conditions Medicines Fund was established to pay for the treatment of these disorders. In October 2014, the New Medicines Fund (NMF) superseded and enlarged this fund to cover the expense of orphan, ultra-orphan, and end-of-life medications for patients. In circumstances where a medicine has not been approved by the Scottish Medicines Consortium (SMC), the NMF can be used to help pay for therapy that has been agreed upon on a "case-by-case" basis for a specific patient through PACS Tier One and PACS Tier Two.
The availability of medications used in the final stages of life, as well as orphan and ultra-orphan drugs, has dramatically improved since the NMF was created. The goal of the fund is to eliminate the potential financial barrier to expanding patients’ access to innovative medications. This fiscal year, the Scottish government anticipates disbursements from the NMF to total £50 million (Scottish Government 2022).

While NICE judgments are generally adhered to in Wales, the All-Wales Medicines Strategy Group (AWMSG) makes some choices for the Welsh National Health Service (Cancer Research UK 2019). The Welsh Government has its own New Treatment Fund. This fund speeds access to novel treatments. The New Treatment Fund requires the suggested drugs to be provided "as soon as generally practicable" and within 60 days after any positive recommendation. After three years of the New Treatment Fund, the average time for newly-recommended medicines to become available to patients dropped by 85%, from 90 days to 13 (Boldero et al. 2021).

In 2018, Northern Ireland’s Department of Health announced measures to expand access to new cancer and other medications. Patients in Northern Ireland have the same access to cancer medications as patients in other UK regions. Medication authorised by NICE for use through the Cancer Drug Fund in England is similarly available in Northern Ireland, in accordance with existing provisions for Northern Ireland endorsement of NICE guidelines (Department of Health 2018b).

Similar to the existing Cancer Drugs Fund (CDF), the Innovative Medicines Fund (IMF) would expedite the development and implementation of promising medicines, regardless of their cost or whether or not they have been authorised for routine use by the NHS. It will pay for
treatment for extremely rare and hereditary disorders that could save lives. Both the CDF and IMF will get approximately £680 million per year from the government. As with the CDF, the IMF will allow for the prompt prescribing of newly approved medicines even before they have been given their final approval by NICE, the advisory body that evaluates the cost-effectiveness of pharmaceuticals used by the NHS (the National Institute for Health and Care Excellence). During the time that NICE is analysing the collected data, patients would have access to the treatment (BBC 2022).

While interview participants were aware of interim funding, e.g., CDF and IMF, in England, they were either not aware of or not sure about the same kind of arrangements in Scotland and Wales.

**Individual funding requests**

Treatments that are not routinely provided by the NHS or have not yet been appraised by NICE in England and Wales or the Scottish Medicines Consortium (SMC) in Scotland may be prescribed through individual funding requests. All around the United Kingdom, various terms are used to refer to individual requests for financial aid (Multiple Sclerosis Trust 2021).

England – individual funding request (IFR)

Scotland – individual patient treatment request (IPTR)

Wales – individual patient funding request (IPFR)

Northern Ireland – individual funding request (IFR)
Private Insurance in the UK

As the UK has a publicly funded healthcare system, new treatments have to go through national, regional, or local mechanisms before they can be used. However, if any treatment is not made available through routine funding, it can be paid for through private insurance, e.g., Novo Nordisk's antidiabetic drug, GLP-1. In 2015, an estimated 10.5 percent of the U.K. population had private, voluntary health insurance, with nearly 4 million policies held at the beginning of 2015. In 2016, voluntary private health insurance accounted for 3.3 percent of total health expenditures (Tikkanen et al. 2020).

6.1.6 Objective 6: key challenges or barriers for access to medicines situation in UK.

Access to innovative medicines continues to be challenging across therapeutic areas and indications, despite numerous targeted efforts to ensure the availability of medications and accelerate patient access to innovative medicines continues to be challenging across therapeutic areas and indications, despite numerous targeted efforts to assure the availability of medications and accelerate patient access (Kamphuis et al. 2021).

Two recent UK government papers indicate areas where further progress is needed if the UK is to retain its gold standard position in bio sciences and become an autonomous powerhouse post-Brexit. MHRA’s Annual Report (MHRA 2022) and the Life Sciences Competitiveness Indicators Report (GOV.UK 2022), which are clinical trials, international collaboration, and innovation in medicine. Noting the ABPI’s dismay at the UK’s performance in several life sciences competitiveness indicators, developments since the reference period were analyzed, as were substantial events on the horizon that should impact those metrics in the year ahead (Hanks 2022).
Qualitative data suggest several challenges, such as the NICE HTA process and methodological capacity to appraise and assign an appropriate value to all categories of medicines, the pricing of medicines, evidence data packages, and the transition following Brexit. Other challenges included the pharmaceutical spending budget, human capacity and resourcing, the healthcare system's lack of capacity for medicine uptake, market access decisions made at an above-country level, non-uniformity in decision making, the government's drive to establish the UK as a centre of innovation, the quality of trials, and the use of digital technology. These challenges are discussed in order of the level of emphasis placed on them by the study participants.

**NICE’s HTA process and methodology**

The pharmaceutical industry’s research and development of medications has altered drastically in the past decade. Novel, potentially curative medicines are being developed to treat patients early in the illness pathway. These drugs have evolved from long-term chronic conditions and late-stage cancers to complex sub-diseases with tiny patient populations. These developments and how evidence is generated can complicate NICE appraisals (ABPI 2021). Since NICE’s inception and the last time its processes were revised, much new information has become available, altering the health and social care systems. There is pressure for medicines to be made available more quickly, sometimes with a lesser evidence base than was previously the case, and evaluating novel approaches (such as individualised medicine and cell therapies) can be difficult (ABPI 2021).

In line with qualitative data, the published literature brings several methodological and process challenges, such as strict reimbursement criteria and a lack of flexibility in the HTA
system, particularly around ICER thresholds, the cost per QALY mechanism, increasing
demand for HTA and pressure for rapid assessment, pressure to evolve existing HTA
methods and processes, the cost of HTA, and how to use process innovations including big
data and machine learning to improve efficiency and speed.

Using a grading system for evidence when making recommendations was seen as a
challenge. In particular, it was hard to figure out how to use these systems when turning
research findings into conclusions in HTA reports. Other issues that were discussed included
figuring out the best way to measure outcomes, coming up with a cost-effectiveness

In the UK, the Health Technology Assessment Innovation Laboratory is a new research and
development space (HTA Lab). The HTA Lab will use collaborative and innovative techniques
to discover solutions to complex HTA concerns—disruptive new health technologies and
larger methodologies, processes, and policy issues. It will help solve present and future
health concerns by putting innovation into practice (Crabb 2022).

**Pricing of medicines**

Pharmaceutical pricing is a critical challenge for all countries (Hanks 2022). Innovative
medicines coming to the market are too expensive for many patients, even in developed
countries, leading to rising inequities in access and care. Budgetary pressures force payers
and insurers to make tough choices, hurting patients and innovation (Hanks 2022). Precision
medicine presents an even bigger challenge to payers, as the price of many drugs in this
category is likely to be very high. An additional difficulty for payers is the increasing value of
diagnostic testing. When drugs were employed to treat all patients with an illness,
diagnostic testing had little utility in comparison to the drug. However, while diagnostic testing for precision medicine can help select which patients will benefit from treatment, it can significantly limit the number of people who use a treatment.

Pricing is another important area, and it’s not just about companies being able to offer prices that make it easier to get reimbursed. There are other barriers and challenges that make implementation difficult.

If there is complex value-based pricing scheme, the need to ensure that the system is set up well enough to capture the data. Value-based drug pricing is a kind of contract between a pharmaceutical company and a purchaser or payor that relates drug payment to the drug’s value, usually assessed by patient outcomes or health care expenses. Initial drug prices are established using data relevant to the drug’s value; drug prices are adjusted after purchase or use to reflect the value received; or purchasers or payors are compensated for the impact (e.g., compensation for costs of treating atypically high adverse events related to drug use). (Brunts and FETHKE 2017)(Group 2019).

As a possible alternative to traditional discounts (like volume-based discounts), value-based drug pricing arrangements can be harder to manage and require more resources, while the benefits are not always clear. There's no precise "recipe" for implementing value-based drug pricing. While VBP might provide a win-win situation for all stakeholders, a failed VBP programme fails all parties. Pharmaceutical companies, health care purchasers, and payors should consider whether value-based medication pricing corresponds with their strategic objectives and ensure any proposed agreement achieves those objectives in accordance
Data Packages

According to a qualitative study, the problem of insufficient data is further complicated due to the divergent data requirements of HTA bodies and the generation of evidence for rare diseases. Consequently, it is challenging to generate a data set that is acceptable to all HTA bodies.

Most problems with HTA of complex health technologies have to do with not having enough data, not with how complicated the health technologies are. As the number of complicated technologies grows, it becomes more important to find new ways and rules to help HTA make decisions. (Hogervorst et al. 2022).

Transition following Brexit

Shared regulatory frameworks at the EU level have made it possible for patients to receive treatment faster. Even though Switzerland and the EU have a number of bilateral trade agreements, Switzerland gets new medicines on average 157 days after the EU. On average, new medicines hit the market in Australia and Canada 6–12 months after they do in the EU or the USA (Brexit Health Alliance 2018).

According to our qualitative study, there is uncertainty with regard to regulatory processes as regulatory responsibilities in the UK have now shifted from EMA to MHRA following Brexit. With this shift, companies face the challenge of an additional regulatory submission
for marketing authorisation to the MHRA, which presents a risk or opportunity for timely filing or sequence of regulatory filings in the UK and a resource burden.

According to our qualitative study, the implications of resource impact are not only for pharmaceutical companies but also for the MHRA. In the post-Brexit area, MHRA's new working model is emerging and offers more collaboration with other regulators through various initiatives, e.g., Reliance and Project Orbis. Progress is also seen in early and closer cooperation between various stakeholders within the UK, i.e., regulatory HTA bodies, and payers, through initiatives such as ILAP and EAMS.

Another Brexit-related challenge that could impact access to medicines is parallel trading and imports. In its response to a government consultation on the future of the UK's intellectual property rights regime, the National Pharmacy Association pointed out a number of benefits and recommendations about parallel trade. Parallel trade has been used to deal with medicine shortages in the UK, making sure that patients always have access to medicines that can save their lives.

The NHS pays less for a number of medicines due to parallel trade, which frees up money to pay for more services elsewhere in the NHS. While community pharmacies buy medicines for the NHS, the savings are passed on to the taxpayer through contracts that pharmacies all over the UK have with the NHS. This means that the ultimate winner of this trade is the taxpayer. Parallel trade can make sure that a patient gets a drug that has gone through the full licencing process when there is no other licenced option. This is a important issue in Northern Ireland, where uncertainty about the Northern Ireland protocol has resulted in challenges related to medicine shortages (InPharmacy 2021).
UK as the centre of innovation and access

The UK government has a desire to establish the UK as a centre of innovation and access. In context of the Brexit implications discussed above and the strained economic situation following the COVID-19 pandemic, this goal has become more challenging.

Pharmaceutical spending

Access, availability, and affordability are the "three A's" of medicine access. All these factors affect how well medicines reach patients. A limited health budget is one reason for the lack of availability or access. The idea of a product or service being "affordable" is more of a relative one. It depends not only on how much it costs but also on how much money is available and who is paying. Since UK health care is paid for by the government and patients don't have to pay much for prescription drugs, it's more important to look at how affordable it is for payers.

Pharmaceuticals spending is a part of the healthcare budget in the EU, and varies from 8% to 24% of healthcare spending across countries. This proportion has not changed much in the last 20 years, even though the use has increased. Spending on pharmaceuticals makes it less likely that a patient will need long-term care in an inpatient setting. It also prevents and treats diseases in patients who would otherwise enter the system with worse outcomes, which would lead to large direct and indirect costs (Allvin 2022).

Non-pandemic healthcare, including pharmaceutical funding, is likely to be impacted as a result of the COVID-19 pandemic and the massive resources poured into combating the virus. The details of the UK healthcare budget showed that overall spending on the NHS will
go down in 2021–22. The total amount spent by the Department of Health and Social Care, including funding for COVID-19, will be £169.1 billion, which is less than the $199.2 billion spent in 2020-21 (Dowd 2021).

The new NHS Commercial Framework for New Medicines is designed to make it easier for the NHS, industry, and the National Institute for Health and Care Excellence to discuss issues related to value, affordability, and transactability. It also aims to get the NHS, industry, and the National Institute for Health and Care Excellence to work together earlier and more effectively. It is hoped that the new framework will help patients get access to medicines (MAP Insights 2021).

Since 2014, branded manufacturers have been required to pay the UK government rebates in order to recoup the difference between the pharmaceutical budget and actual spending. This obligation is imposed both statutorily and through a voluntary programme (Rodwin 2021). Currently, payments under the statutory scheme are set at 10.9% of net income. In response to a consultation held in March 2022, the Department of Health and Social Care stated that payment rates would rise to 14.3% in July 2022 and 24.4% in 2023. The manufacturers' trade association, the Association of the British Pharmaceutical Industry (ABPI), has expressed concern about the "unprecedented" tax rate (Care 2022).

Human capacity and resourcing

A health workforce is necessary to make access to health products possible (WHO, n.d.) According to a survey of EU HTA bodies, 30% of agencies cited a lack of human resources as their most significant challenge (Rourke et al. 2020). MHRA recently laid off 300 employees due to budget cuts. Medical regulation experts say that the cuts may limit the ability to keep
up with EU developments (vanessa zainzinger 2021). The UK pharmaceutical industry employs 67,000 people directly, according to the ABPI. As in many specialised sectors, talent is limited. Pharmaceutical companies compete for the same candidates. Understaffed departments become fatigued and overstretched as roles remain unfilled (Manlises 2021).

According to our study’s qualitative data, human capacity and resourcing are challenges that impact all stakeholder levels and are often overlooked by pharmaceutical companies, regulatory bodies, HTA bodies, and payers.

Lack of capacity of healthcare system for medicine uptake

The availability of medicines in a given country does not guarantee their accessibility to its citizens. It is not enough that a medicine is on the public reimbursement list and has made it to a pharmacy or hospital; it still needs to make its way to the patient, usually by means of a prescription. Qualitative data suggests a lack of capacity in the healthcare system for the uptake of medicines as a key challenge.

A delay in incorporating new drugs into clinical guidelines may contribute to limited uptake since contracts must be negotiated with individual hospitals within the framework of individual budget constraints after national reimbursement decisions have been made (Vintura 2020b).

The United Kingdom’s ranking for medicine uptake varies across disease areas and medicine categories. This is true for the majority of other countries as well. For example, as we are heading in the direction of precision medicines, in this approach the target population for a treatment is narrowed. The question arises as to whether the health care system has facilities in place to appropriately identify these patients through genomic testing. According
to qualitative data, since the uptake of cancer medicines is facilitated through the cancer drug fund, there are more challenges for non-cancer medicines. However, this is expected to be addressed by the recent introduction of an equivalent fund, i.e., the IMF, for non-cancer medicines.

There is no single clear determinant of a country’s level of drug usage. However, it appears that a variety of factors influence the UK’s level of drug use when compared to other countries. These encompass health, economic, organisational, and cultural issues and will vary according to disease areas that are worthy of further investigation (Richards 2010). This challenge has been officially acknowledged, and NHS England recently established Academic Health Science Networks (AHSNs) to speed-up the uptake and diffusion of new medicines (Freeman 2015). There is a more in-depth discussion to pertaining to the uptake under objective 5, that is, "Medicine uptake post-licensing and/or health technology assessment recommendation."

**Market access decisions global**

Although local affiliates play their part in the preparation of submissions to HTA bodies, HTA submission strategies and filing sequence decisions are made at the above-country level (Wang et al., 2020b). While local affiliates play their part in the preparation of submissions to HTA bodies, HTA submission strategies and filing sequence decisions are made at the above-country level.

**Non uniformity in decision making**
The lack of an explicit framework on the way HTA evidence is used in the decision-making process is the most significant barrier to access in Europe, while the existence of such a framework is one of the most significant enablers (Cheung et al. 2018). As a result, variations in HTA systems intrinsically affect the availability of medicines. There is evidence that different countries have distinct values, as shown by the fact that HTA processes within jurisdictions have undergone numerous shifts throughout time and that there are constant international disparities in HTA practises.

Due to differences in HTA systems and procedures (such as routine requests for economic analysis or budget impact), evidence requirements (such as acceptance of early phase clinical studies, use of RWE and surrogate endpoints, and selection and acceptance of comparator therapy), willingness to pay thresholds, and the way evidence is interpreted, coverage decisions and evaluation criteria can vary among EU member states (Kamphuis et al. 2021).

**Quality of clinical trials**

It is difficult to design studies that meet the needs of regulators, HTA bodies, and payers all at once. The use of correct endpoints and appropriate trial designs could help with this (e.g., basket trials, umbrella trials, among others). This is made more difficult by the challenges associated with recruiting patients and carrying out clinical trials (Kamphuis et al. 2021).

There are several challenges in conducting clinical trials, including the management of ethical and regulatory systems, the recruitment of patients, lack of funding, the lack of qualified staff, the lack of infrastructure, a lack of public understanding, a lack of motivation, and a lack of time (Varse et al. 2020). Despite these challenges and complexities, in 2021,
there were 56% more oncology trial starts than in 2016, and most of them were for rare cancers, which have higher success rates despite being harder to treat (IQVIA Institute for Human Data Science 2022).

**Digital Healthcare**

The use of digital technology is growing while simultaneously becoming more affordable. Both the demand and the cost of healthcare are on the rise, which presents issues for the majority of economies worldwide concerned with health care. The use of digital technology to address these challenges appears to be an obvious necessity; however, the healthcare industry lags behind other industries in terms of technology application. There is a great deal of promise for digital technology to improve many different elements of medical treatment, including access to different medications (karen Taylor 2015).

Digital health empowers users and patients to access healthcare at the point of care or remotely. Digital health allows healthcare practitioners to improve their knowledge, abilities, and patient care. Legal, ethical, infrastructural, human, and material resources; training; education; and attitudinal, cultural, organisational, and behavioural issues exist when using digital health solutions (Shorbaji 2021).

We’re headed toward a world where health care will be digital, e.g., increased management of patients at home rather than in hospitals. As this transformation occurs, pharma companies will be expected to enable the remote monitoring of patients on their drugs, such as by establishing applications to enable patients to manage themselves at home. There is a greater expectation that pharmaceutical companies will manage the treatment
pathway rather than simply providing innovative treatments and leaving it to the NHS or payers to optimise treatment use.

6.2 Study Limitations

This research lacks input from certain stakeholders, including HTA bodies and payers’ organizations. It is hard to get this data due to confidentiality issues. This is a rapidly evolving environment, and some of the collected data may not be a true representation of the situation at the time of reporting.

Due to the fact that the material for this study came from a few pharmaceutical companies, the findings were interpreted using the perspective provided by these companies rather than the perspective of the entire pharmaceutical industry. However, we feel that these companies are reflective of the pharmaceutical industry and that the HTA approaches taken by these companies are a good predictor of the approaches taken by other businesses. When attempting to understand the jurisdictional data, one must exercise caution because these results do not fully reflect the overall performance of the HTA entities.

6.3 Conclusion

Based on in-depth literature readings, document analysis, and interviews with pharmaceutical industry professionals, this research work examines the prospects for accessing medicines and the obstacles that stand in the way of doing so. It focuses on the market in the UK but puts it in the context of the rest of the world. It does this by using successful business models from both the UK and other countries.

The purpose of this research is to spark conversation and provide readers with examples of various challenges and opportunities that impact access to medicines and that may apply to
their own circumstances. To address the identified gaps and challenges, particularly those pertaining to timelines from licencing to reimbursement of medicines, licencing versus reimbursement recommendations, relevant insights into the variability of reimbursement decisions across HTA bodies and countries, and adoption of medicines, additional research is required. This will allow for a better understanding of the factors that act as both barriers and facilitators for the adoption of new medicines into clinical practise.

This research confirms the existence of a significant gap between licencing and reimbursement. It also identifies the factors that will have an impact on this gap in the near future, both positively and negatively. Research evidence suggests that pharmaceutical companies, regulators, HTA bodies, and payers think differently and have different needs. The trend toward high-tech and complicated medicines, small patient populations, limited data sets, more budget cuts, HTA bodies' need for long-term data, poor adoption, and optimised HTA recommendations were the key things that were believed to make the gap between licensing and reimbursement of medicines bigger. Focus on more specific and targeted therapies, interim funding in England, Wales, and Northern Ireland (CDF and IMF), and new processes like ILAP and NICE methods review (change in end-of-life criteria to severity criteria) were thought to help close the gap between medicines being licenced and reimbursement of medicines.

It includes suggestions to reduce this gap between licencing and reimbursement. This study suggests that encouraging access primarily through interim arrangements followed by more formal HTA, exploring and addressing the challenges of medicine uptake at the local level,
and allowing access at the point of licence and imposing restrictions later could help close the licensing-reimbursement gap.

While the time from licence approval to reimbursement widely varies, this time lag appears to be decreasing, and it is likely to be reduced further in the future. This research also shows variability in HTA recommendations and reimbursement across countries in the UK. It also explores the variability further by discussing the key drivers that play their part in this variability, and it also discusses the trend for variability and suggests ways to decrease this variability in HTA recommendations and reimbursement across countries in the UK. It concludes that positive HTA recommendations do not necessarily result in positive reimbursement decisions, as these decisions are made at the regional level.

It concludes that the rate and extent of medicine uptake do vary, and, in some cases, they are considerably lower due to challenges in implementation. Some of the key challenges with access to medicines in the UK include the NICE HTA process, methodology, and ability to evaluate and give the right value to all types of medicines; the prices of medicines; evidence data packages; and the transition after Brexit. Other challenges were pharmaceutical spending, human capacity and resources, the inability of the healthcare system to use medicines, the decision-making process for market access, the government's push to make the UK the centre of innovation and access, the importance of trials and data quality, as well as the use of digital health technologies and the appropriate endpoints.

Future recommendations to improve access to medicines in the UK

Even though the pharmaceutical industry is important, governments are mostly in charge of making sure that health care systems work. The healthcare system is the main way that
people can get access to all kinds of health care, including new medicines. Healthcare systems must ensure that patients can afford them, that they are sustainable for everyone involved and that they have the flexibility to deal with new diseases, changing populations, new scientific discoveries, and changing technologies. We can make progress on this global challenge if we use the skills, strengths, and resources of all stakeholders to solve these problems.

Particularly, the Health Technology Assessment (HTA) system in the UK might be further adapted to impending issues and ought to evolve to increase access to innovative medicines. In today's rapidly changing HTA environment, it is important for HTA bodies to work together, and the regulatory and HTA processes should be better coordinated to speed up access to medicines.

Policy implications of this work

This thesis serves as a helpful stimulus for stakeholders across the UK in their efforts to overcome problems, take advantage of opportunities, and adopt new initiatives. We also expect that the findings from this research will provide useful background information and prompt interesting questions that can help direct future studies in this area.

6.4 Future research

The following are some potential areas for further investigation:

- This research was based on in-depth literature readings, document analysis, and qualitative interviews with pharmaceutical industry professionals. Further qualitative research on access to medicines involving other key stakeholders, e.g., HTA bodies, payer organizations, and patients, is needed.
• Investigation of the impact of new initiatives either from the pharmaceutical industry, government health departments, HTA bodies, regulatory bodies, or payer bodies (NHS, CCGS, ICSs, and health boards) on access to medicines. For example, the government initiated an "accelerated access review" in 2014 to speed up NHS patients' access to innovative medications, equipment, and diagnostics. NHS England formed the Accelerated Access Collaborative after the review to speed up the adoption of novel treatments (Thornton 2021)(HM Government 2022).

• The government's health-related levelling-up programme aims, among other things, to close the gap in healthy life expectancy (HLE) between areas with the highest and lowest HLE by the year 2030 and to increase HLE by five years by the year 2035 (Ralston et al., 2022). It will be fascinating to see what effect the UK government's equality-focused "levelling up" agenda has on the country's healthcare system, in particular the access to medicines situation across the UK.

• While in the United Kingdom, NICE has a clear impact on the HTA and reimbursement of medicines in Wales and Northern Ireland. It may be fruitful to investigate the extent and means by which decisions made by one HTA body, such as NICE, can influence another HTA body, such as SMC, and vice versa.

• A study comparing any aspect of access to medicines in a leading EU country or countries, and how the results of such studies can be used to improve access to medicines in the the UK.

• According to Alam et al (2018), while the elimination of co-payments increased dispensing rates in Wales, the effect was not significant. However, the current cost of
living crisis warrants further investigation to study the impact of co-payments on access to medicines in England.
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Appendices
Appendix 1: Search Terms and number of Search Results (‘Hits’) by Database or Journal

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Appendix 2: Summary of studies reported access to medicines in the UK and EU region.
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<th>Author, year of publication</th>
<th>Data collection period</th>
<th>Location</th>
<th>Theme</th>
<th>Aims/objectives</th>
<th>Study design</th>
<th>Assessment of access</th>
<th>Key findings</th>
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<tbody>
<tr>
<td>Ragupathy et. Al., 2012</td>
<td>2007</td>
<td>Australia, New Zealand, UK, US</td>
<td>1. Access to Medicines</td>
<td>To compare access to medicines under nationwide single-payer systems in 4 countries in terms of the number of registered medicines, the age of the medicines and the number of innovative medicines that are licensed &amp; then funded.</td>
<td>Observational study</td>
<td>All products in each country's principal prescribing reference were considered for the research. Dates of registration and ATC codes were used to categorise all products. Each medicine's 'best-case' licencing and subsidy, as well as its date of initial registration, were calculated by collapsing products by their respective ATC codes..</td>
<td>NHS financed the most, newest, and most innovative drugs. PHARMAC sponsored the least innovative and oldest drugs in New Zealand. These systems' cost-containment and budgetary constraints may explain these disparities.</td>
</tr>
<tr>
<td>Drummond, et al., 2014</td>
<td>Sep 2003 to Jan 2012</td>
<td>Europe including England</td>
<td>Health Technology Assessment (HTA)</td>
<td>To review different approaches in Europe &amp; UK for rewarding the value added by new medicines.</td>
<td>Descriptive review</td>
<td>The study compares and contrasts the English and French methods, weighing the merits and negatives of each in terms of the quality of their evaluations and the viability of their implementation.</td>
<td>England and France evaluated new drugs similarly. England's method is more transparent and encourages political debate. France's cost-effectiveness criterion and England's confidential price</td>
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<tr>
<td>Authors</td>
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<td>Countries</td>
<td>Methods</td>
<td>Study Type</td>
<td>Findings</td>
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<tr>
<td>Salas-Vega, S., Bertling, A., &amp; Mossialos, E. (2016)</td>
<td>2009 and 2013</td>
<td>Australia, Netherlands, Sweden, and the UK</td>
<td>Health Technology Assessment (HTA)</td>
<td>A Comparative study</td>
<td>To study the HTA review processes and drug listing verdicts from 4 HTA agencies in Australia (PBAC), England (NICE), the Netherlands (CVZ; ‘Zorginstituut Nederland’, and Sweden (TLV). It was determined which medications had been evaluated by each of the four HTA agencies using a methodical procedure. This study employed as a common sampling frame 43 medications for which appraisals were accessible from HTA agencies in Australia, the Netherlands, Sweden, and the United Kingdom. There is public advice accessible for health technology evaluation in all four nations, and these evaluations are based on the evidence given by the maker. Additionally, therapeutic assessment groups are utilised for independent evaluations in the United Kingdom. There is a willingness to pay for an explicitly stated ICER threshold in England. There is a fair amount of variation among the various settings, despite the negotiations are converging.</td>
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<tr>
<td>Bending, M., Hutton, J., &amp; McGrath, C. (2012).</td>
<td>between 2005 and 1st Jan 2010</td>
<td>France, Scotland</td>
<td>2. Health Technology Assessment (HTA)</td>
<td>The objective of this study was to compare the medicine reimbursement systems in France and Scotland.</td>
<td>A Comparative Study</td>
<td>The purpose of this research is to examine how health economic analysis contributes to reimbursement recommendations for medicines evaluated by various agencies and to identify any discrepancies in approach between these organisations.</td>
<td>When it comes to drug recommendations, the French agency Haute Autorité de Santé (HAS) is more frequent than SMC. Local clinical guidelines and the selection of comparators may account for some of the observed variation in recommendations. Manufacturer-set prices are contested by SMC, and reimbursement decisions are made on clinical and economic data. In terms of payment, HAS decides based...</td>
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</table>
on clinical data, whereas price is determined independently through CEPS deliberations. There is a difference in manufacturer incentives between the two methods presented above.

O’Neill, P., & Devlin, N. J. (2010). From 2006 to the end of 2009 in England. To report an attempt to develop a robust and defensible means of measuring and describing the degree of patient access in mixed NICE verdicts. There was a compilation of contradictory court decisions from 2006 through the end of 2009. It was determined using the formula: $M = \frac{p}{P} \cdot 100$, where $M$ is a measure of the level of patient access, $P$ is the set of patients identified in the guideline as Potential candidates for treatment, and $p$ is a subset of those patients, for whom In little under three-quarters of mixed conclusions, NICE recommended use for fewer than half of licenced patients, and in nearly one-third of such verdicts, NICE approved use in less than 10 percent of prospective patients.
Cylus, J., & Papanicolas, I. (2015). EU Countries 4. Access to Medicines To study variations in perceptions of access to health care across and within 29 European countries. Observational study Study examines the likelihood that an individual will perceive that they will face difficulties receiving health care in the next 12 months if they need it (N = 51,835) using data from the 2008 round of the European Social Survey. People in the region have wildly varying levels of access to healthcare, including pharmaceuticals. People of all socioeconomic backgrounds face difficulties gaining easy access to the medicines they need. It’s also possible that views of barriers to medication availability stem from other factors, such as the quality of treatment provided or the length of wait times for medical services.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Countries</th>
<th>Health Technology Assessment (HTA)</th>
<th>Study Objective</th>
<th>Methodology</th>
<th>Findings</th>
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<tr>
<td>Nicod, E., &amp; Kanavos, P.</td>
<td>2007-2009</td>
<td>England, Scotland, Sweden, Canada, and Australia</td>
<td>5. Health Technology Assessment (HTA)</td>
<td>To identify diverging HTA recommendations across five countries, understand the rationale for decision-making in specific therapeutic categories, and suggest ways forward to minimize these inter-country differences.</td>
<td>Comprehensive review of two case studies and a comparison of HTA recommendations for 287 drug-indication combinations reviewed by five countries between 2007 and 2009. The degree of agreement was calculated using kappa scores. Correspondence analysis was used to investigate possible connections.</td>
<td>Differences in priorities, therapeutic area, levels of evidence, perceptions of value, strategies used to handle ambiguity, and the capacity and motivation to consider and implement risk sharing agreements may all play a role in shaping HTA procedures, as shown by the study’s findings.</td>
</tr>
<tr>
<td>Beletsi, A., Koutrafouri, V., Karampli, E., &amp; Pavi, E.</td>
<td>January 2000 to February 2015</td>
<td>England, Germany, France, and Sweden, Poland, Bulgaria, Hungary, and Romania</td>
<td>6. Health Technology Assessment (HTA)</td>
<td>To compare how HTA is implemented in the procedures for reimbursement of medicines in selected countries at different levels of maturity in the application of HTA.</td>
<td>Group A consisted of the &quot;earlier&quot; adopting countries (which included England, Germany, France, and Sweden) whereas group B consisted of the &quot;more recent&quot; adopting countries (which included the rest of the selected countries) (group B: Poland, Bulgaria, Hungary, and Romania). An analytical framework was utilised for the Efficiency, safety, comparative efficacy, and cost-benefit analysis are only some of the factors that can be used as evaluation criteria. The primary goals of HTA adoption in a group of countries that includes England are to increase the quality of treatment, guarantee equal access, and spend resources efficiently. Even though these</td>
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purpose of analysing and contrasting HTA processes. Less developed nations have HTA bodies and norms in place, they frequently follow the advice of more developed nations. In a study conducted by (Beletsi et al. 2018)
The research looked into the percentage of recently approved medicines that were covered by health insurance in a few European Union and Japanese countries. Comparisons of EU countries' reimbursement rates to Japan's for similar products.

When compared to other developed countries like France, Germany, and the UK, Japan was found to have more people covered by health insurance and less obstacles to receiving care. The Japanese reimbursement process took 66 days to begin once the licence was granted. In this case, though,
the time period was 2014 and lasted for a total of four months. Drug prices in Japan and the chosen EU nations did not differ much.

<p>| Ferrario, A., &amp; Kanavos, P. (2015). | 2003 - 2012 | Belgium, England, the Netherlands and Sweden | 8. Access to Medicines | To develop a conceptual framework for MEAs and to test it by exploring variations in MEAs implementation across countries and over time as well as their governance structures. | A comparative analysis | The websites of HTA agencies, health insurers, and governments were mined for information on the medicine-indication pairings subject to a MEA, the types of MEAs adopted, and their governance structures. Materials from a survey of MEAs across Europe, in addition to what was learned through networking. Starting with the initial official MEA implementation date for each country and continuing through December 2012, all MEAs reported by countries were included in the analysis. | It appears that the motivations behind the adoption of various MEAs are consistent from one country to the next. It is unusual for MEAs to be adopted internationally for well-studied medications. There are several forms of the same medicine in nations where MEAs are in place. It's likely that differences in national health care systems account for the observed disparity in MEA implementation. The degree of uncertainty, the ability to pay, the relative cost-effectiveness, and the effect on the overall budget are |</p>
<table>
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<tr>
<th>Author(s)</th>
<th>Country</th>
<th>Health Technology Assessment (HTA)</th>
<th>Methodology</th>
<th>Description</th>
</tr>
</thead>
</table>
| Linley, W. G., & Hughes, D. A. (2013) | Wales | Health Technology Assessment (HTA) | A Discrete-Choice Experiment | To explore the preferences of All Wales Medicines Strategy Group (AWMSG) appraisal committee and appraisal sub-committee members for specific new medicines adoption criteria and to explore the external validity of respondents' stated preferences and the impact of question choice options upon preference structures in DCEs. Committee members' preferences for incremental cost effectiveness, quality-adjusted life years (QALYs), estimated number of treated patients per year, disease impact prior to treatment, and ambiguity in economic data submitted for novel drugs against current NHS therapy were evaluated. Subjects were asked to rate 28 hypothetical pairs of new drugs, making a main forced choice between each pair and a secondary choice that allowed for either, neither, or both new medicines to be selected. Success of the resulting models was measured against earlier decisions made by the AWMSG. Members of the AWMSG Committee are flexible in exchanging medicine's cost effectiveness and QALY gains for other considerations. This result suggests that recommendations for the use of pharmaceuticals in Wales take into account factors other than economic efficiency and QALY maximisation. The external validity of our DCEs is supported by the fact that the specific preferences of AWMSG committee members look congruent with their actual decision-making behaviours. Complex decision-making processes underpin HTA recommendations, with a wide range of additional factors associated with the variants in the MEAs.

Patient Access Schemes, Managed Entry Agreement and Risk-Sharing Agreements

To analyze the extent to which NICE drug appraisals influence the construction of PAS and what rationale underlies the variety of approaches to their design.

Patient Access Schemes (PAS) developed as part of the NICE HTA process as of December 2010 were studied in this study.

NICE HTA is the driving force behind PASs, which aim to clarify any doubts about the efficiency of a given treatment and reduce associated costs. These programmes in the United Kingdom are monetary in nature, and rather than reducing list prices, concessions and refunds are agreed upon. The study did not find evidence that manufacturers were motivated by profit in these partnerships. There is a need for a procedure that is open and can aid in a fair evaluation of PASs.
schemes because they are not easily understood in the context of reference pricing (due to the confidential discounts, rebates agreed with the payors in PAS schemes).

Nicod, E., & Kanavos, P. (2015). Dec 2012 England, Scotland, Sweden and France 10. Health Technology Assessment (HTA) To develop and pilot such a methodological framework that allows for a comprehensive and systematic identification and comparison of the key factors that influence coverage verdicts in different stages of HTA processes. A mixed methods study The methodological framework in the form of an instrument development design was created and piloted using a sequential exploratory mixed methods approach. Two orphan medications were used to test the methodology, which was based on the three steps of the HTA procedure: (a) gathering evidence, (b) analysing that data, and (c) considering how that analysis would affect the final conclusion. The purpose of this study was to investigate the contextual variation in HTA recommendations, and to do so, a well-structured framework was presented and guided by this research. This structure is comprehensive and sheds light on how the chosen case studies’ decisions were made. Work is underway to improve the framework’s external validity so that it can be used with a broader range of

Jan 2011 to Dec 2013
Spain, England

11. Health Technology Assessment (HTA)

To assess the differences between NICE and the Spanish bodies in terms of their respective processes. We compare the verdicts concerning cancer medicines in the assessments made by NICE/Single Technology Appraisal with assessments made by MADRE methodology.

A comparative Study

All of the NICE-evaluated cancer drugs, all of the MADRE reports submitted through a centralised reporting system (GENESIS), and all of the MADRE, Catalonia, and Andalusia reports (GFTHA). We examined the number of drugs evaluated, the decisions made by NICE and the Spanish organisations, and the lengths of their respective timetables.

HTA agencies in both countries encourage the same practices, such as only appraising carefully selected drugs. This research reveals that because of the greater availability of HTA bodies and the less complex nature of their procedures, the Spanish have a larger share of the total number of medications reviewed compared to NICE. NICE’s rejection rate is higher than that of the Spanish review boards. Spanish organisations are more likely to prescribe cancer treatments for subpopulations of individuals where better outcomes can be gained, whereas treatments, specialties, and nations.
| Spinner, D. S., Birt, J., Walter, J. W., Bowman, L., Mauskopf, J., Drummond, M. F., & Copley-Merriman, C. (2013). | 2007 and 2010 | Australia Canada, England and Wales | Health Technology Assessment (HTA) | To assess whether different clinical evidence bases may have influenced listing recommendations made by PBAC, CDR, and NICE. | An in-depth case series | From 2007 to 2010, the three agencies gave listing recommendations for nine medications for the same indication. We looked at the evidence that went into each listing suggestion, compared and contrasted the clinical evidence bases that were taken into account, and assessed how much the comments from the HTA body and public opinion on the evidence influenced our findings. | According to the data collected, there were four instances where HTA bodies reached the same conclusion and five instances where they reached different conclusions. The HTA bodies' separate conclusions were based on different sets of evidence. HTA organisations looked at additional trials and sets of comparators while evaluating the same drug. Canadian CDR (Common Drug Review) did not take into account indirect and/or mixed comparisons, in contrast to PBAC (Pharmaceutical Benefits Advisory Commission). NICE applies cost-effectiveness thresholds in its appraisals, resulting in a 'not recommended' judgement in many cases. |

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<th>Findings</th>
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<td>England</td>
<td>Patient Access Schemes, Managed Entry Agreement and Risk-Sharing Agreements</td>
<td>To analyse the potential value delivered by the Cancer drug fund as patient access scheme</td>
<td>Value created for patients and society by the CDF in terms of pharmaceuticals and other medical interventions. There are six criteria that have been used to determine worth. Cost-effectiveness criteria as outlined by NICE and an analysis of real-world data are included. 29 cancer</td>
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The results of this study suggest that the enormous expenditures invested in this programme have not yielded any appreciable benefits for patients. The programme has undergone significant revisions and been rebranded as the managed

Committee) and NICE. CDR and/or NICE may have disregarded trials from their evaluation if the drug or comparator used was not administered in accordance with the terms of the appropriate licence. It was found that the clinical evidence assessed by PBAC, CDR, and NICE for drug-listing recommendations varied widely across the reviewed listing recommendations.
medications that were approved for 47 indications and were available through the CDF as of January 2015 are the topic of this analysis.

It has been shown through analysis of the effects of NICE's restrictive recommendations for medicines that there is a strong correlation between the amount of restrictive verdicts and the financial burden on the NHS. The National Institute for Health and Care Excellence (NICE) may have something to do with this correlation because they take clinical effectiveness and cost-effectiveness into account when approving a drug for marketing in the United Kingdom.

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<tr>
<th>Authors</th>
<th>Year</th>
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<th>Study Details</th>
<th>Data Collection</th>
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<tr>
<td>Mauskopf, J., Chirila, C., Birt, J., Boye, K. S., &amp; Bowman, L.</td>
<td>2013</td>
<td>England</td>
<td>To determine whether reimbursement restrictions recommended by the NICE have impacted the UK NHS budget.</td>
<td>Information was culled from March 2011 cost statements and NICE advice publications. To calculate the maximum and adjusted potential budget impact (PBI) on the NHS, we used data on the number of people living in the UK with an authorised prescription for the new drug and its yearly cost. To evaluate the relationship between the NICE-recommended payment constraints and the PBI while still taking into account clinical efficacy and cost-effectiveness, both descriptive and logistic analyses were utilised.</td>
<td>It has been shown through analysis of the effects of NICE's restrictive recommendations for medicines that there is a strong correlation between the amount of restrictive verdicts and the financial burden on the NHS. The National Institute for Health and Care Excellence (NICE) may have something to do with this correlation because they take clinical effectiveness and cost-effectiveness into account when approving a drug for marketing in the United Kingdom.</td>
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<td>Eva Susanne Dietrich (2009)</td>
<td>2000 to 2004</td>
<td>England, Germany</td>
<td>14. Health Technology Assessment (HTA)</td>
<td>The aim of this study was to study the impact of the National Institute for Health and Clinical Excellence's (NICE's) negative and restricting technology appraisals on the number of prescription items dispensed and the corresponding total net ingredient costs for medicines from 2000 to 2004 in the ambulatory care of the National Health Service (NHS) in England and Wales. The NICE approach could be a role model for Germany.</td>
<td>Thirty-one drugs paid for by the NHS are discussed, including thirteen drugs described descriptively and twenty-one drugs assessed statistically using regression. Information for outpatient care was culled from the British Department of Health's &quot;Prescription-Costs-Analysis-Statistics&quot; (England 1993–2005). Predictions of how prescribing and prices would have evolved without NICE's drug appraisal were established for the twenty-one drugs evaluated using regression analysis. Finally, conclusions were formed as to whether or not NICE's negative and restrictive drug assessments had a dampening effect. Results from this study corroborate previous research showing that restrictive and unfavourable HTA judgements have little effect on reducing prescription rates and costs. Possible reasons for this ineffectiveness include prescribers' unwillingness to follow HTA guidelines. One possible explanation is that the interests of those making decisions in HTA committees and those of the local health service are not aligned. It also shows that local level use of cost-effectiveness evidence is challenging without some significant investment in economic evaluation.</td>
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<tr>
<td>Reference</td>
<td>Study Description</td>
<td>Methodology</td>
<td>Results/Key Findings</td>
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<td>Kleijnen, S., Toenders, W., de Groot, F., Huic, M., George, E., Wieseler, B., ... Goettsch, W. (2015).</td>
<td>Between 8th and 16th January 2013 France, Germany, Italy, England, Austria, Netherlands, Poland and Croatia.</td>
<td>Health Technology Assessment (HTA) To identify the possible barriers and critical success factors for the implementation of European collaboration in the field of relative effectiveness assessment (REA) of medicines.</td>
<td>Information was collected via semi-structured interviews with eight European HTA bodies that evaluate drugs for coverage decisions. Challenges in terms of research methodology, available resources, and challenges in actual implementation are all highlighted in the study. Evaluation quality, timeliness, and collaboration between competent partners across borders were shown to be the most potential success criteria in cross-border evaluations. More fine-tuning of the procedure and approaches is needed for optimum cooperation.</td>
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<td>Ratcliffe, J., Bekker, H. L., Dolan, P., &amp; Edlin, R. (2009).</td>
<td>England</td>
<td>Stakeholders involvement/ views on Reimbursement Process To describe the views of health care decision-makers and providers operating in the UK National Health Service (NHS) concerning the concepts of cost-effectiveness, equity and access through a series of attitudinal</td>
<td>A discrete choice experiment A total of 1456 healthcare decision-makers and providers were given one of three DCE questionnaires, with or without a series of attitude questions. The survey asked respondents to rate how important they Study shows that members' perceptions vary by job and responsibility in various organisations. Women preferred lowering health disparities more than men. Primary Care Trusts, Strategic</td>
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To challenge the widespread assumption that the price of any single drug increases with inflation in the UK, and to calculate the impact on the incremental cost-effectiveness ratio (ICER) of using a more realistic estimate for the future price of individual medicines. A study was conducted to determine the percentage increase or decrease in the true cost of 373 different medicines sold in the UK between the years 1980 and 2006. Only drugs with yearly prescription rates of 500 or more were considered for this study, and only those introduced after 1984. To account for differences in launch year, prescription volume, and British National Formulary. According to the data, the cost-effectiveness of these drugs was even higher than previous NICE assessment results indicated. In light of this, it is possible that some previous NICE decisions with a negative or restrictive consequence could have been reversed and rendered a good decision.

questions and to evaluate the preferences of health care providers in relation to each of these concepts using a discrete choice experiment (DCE). found cost-effectiveness, equality, and access to care to be in the context of several fictitious, highly specialised treatment programmes for cardiovascular disease. Health Authorities, and Department of Health staff preferred programmes that targeted the poor over hospital administrators. Clinical workers preferred reduced waiting times and equity over managerial and non-clinical staff.
| Fischer, K. E., Heisser, T., & Stargardt, T. (2016). | 2011 -2014 | England, Germany, Scotland and Australia | 18. Health Technology Assessment (HTA) | To compare the verdicts of the German Federal Joint Committee (FJC) with three other HTA agencies including the NICE, the Scottish Medicines Consortium (SMC), and the Australian Pharmaceutical Benefits Advisory Committee (PBAC) as comparator HTA agencies. | Case decisions for similar groups of patients rendered by the four regulatory bodies between 2011 and 2014. To begin, verdicts were compared (a) according to their ultimate conclusion, i.e., if a health benefit was recognised, and (b) according to the agencies' decision on comparative effectiveness. Next, we delved into some of the variances in approach taken by HTAs and their causes. | German HTA body verdicts were compared to those of HTA bodies in England, Scotland, and Australia, and the results showed that the German FJC significantly deviates from established HTA agencies, even when merely examining issues of comparative effectiveness. Study finds FJC appraisal is more stringent than NICE, which may be due to differences in agency missions, characteristics, decision-making process, and ramifications of a bad judgement for patient access. |
| Moreira, T. (2011). | 2005-2008 | UK | Stakeholders involvement/ views on Reimbursement Process | To propose an uncertainty-focused conceptual model of the relationship between knowledge practices and political processes in health care rationing. | Case-Study | With a case-study method, this paper investigates the debate over whether or not the National Health Service in the United Kingdom should cover dementia medicines. | Health care needs to be rationed because there aren't enough funds, and this needs to be done in a planned way. It is easier to carry out socially strong decisions than bureaucratic ones. So, when it's hard to come to a decision, the people involved should go out of their way to get the opinions of members, like the general public, who aren't usually part of the decision-making process. |
| Skoupá, J., Annemans, L., & Hájek, P. (2014). | Poland, the Czech Republic, Slovakia, Hungary, Romania, the United Kingdom, France, Germany, the Netherlands, and Sweden. | 19. Health Technology Assessment (HTA) | To compare data requirements and their availability for health economic (HE) evaluations in five countries in Central/Eastern Europe (CEE) (Poland, the Czech Republic, Slovakia, Hungary, and Romania) and five countries in Western Europe. | Market access staff from Pfizer were sent a questionnaire and instructed to fill it out using their own knowledge or with the help of other experts. This survey inquired as to whether or not HE assessment was required for reimbursement claims, the existence | According to the research, HE assessments are necessary in the majority of nations for reimbursement requests. Cost-benefit analysis and budget impact studies are common tools in HE evaluation. At the time of the survey,
Europe (WE) (the United Kingdom, France, Germany, The Netherlands, and Sweden).

- of local HE guidelines, the usage of discount rates for future costs and impacts, the existence of willingness-to-pay levels, and the existence of data sources.

- no guidelines were located for Romania, France, or the Czech Republic. In Sweden and the UK, license holder usually prepares HE evaluations dossiers. Countries like the United Kingdom, Poland, and Slovakia have shown a definite willingness to pay at least some amount. The CE study in the Netherlands, Sweden, France, and Poland must include a comprehensive societal perspective. Even though HE analyses have the same requirements in CEE and WE, researchers discovered discrepancies in the quantity and quality of data available in the two regions.
| Franken, M., Heintz, E., Gerber-Grote, A., & Raftery, J. (2016). | England, Germany, Netherlands, and Sweden | 20. Health Technology Assessment (HTA) | To assess the impact of economic evaluation in four European countries, ranging from those who have embraced it (England, the Netherlands, and Sweden) to one that has largely rejected it (Germany). | Using a standardised approach, we compared how four European Union (EU) countries—including England—applied economic evaluation to reimbursement decisions. For the sake of this analysis, "impact" refers to financing decisions, and more specifically, the decision not to support expensive medications that are deemed not cost-effective. |


| According to the research, HE assessment has not helped limit patient access to costly medications. The debate of clinical effectiveness has been broadened to include cost as a result of economic evaluation, which may have helped some countries negotiate price reductions for some medicines. Given the variety of methods used to evaluate higher education but the similarity of their outcomes, it is likely that most of this work is merely rhetoric. |


| It is noted that HTA bodies have several things in common, such as a concern with clinical efficacy and cost-effectiveness in making decisions. All of these measures |
| Kolasa, K., & Wasiak, R. (2012). | January 1 to December 31, 2008 | Scotland and Poland | 22. Health Technology Assessment (HTA) | To compare Polish and Scottish HTA process in order to elicit recommendations for future development of HTA methodological guidelines in Poland. | Research into the dissimilarities between Polish and Scottish HTA guidelines was conducted. All HTAPol recommendations for drugs released between January 1 and December 31 of 2008 were compared with the public domain was used. As examples, we chose drugs that were evaluated by all four bodies but were given a negative recommendation by just one. The choice of a comparator in clinical and cost-effectiveness studies may be at the root of the discrepancies in recommendations, as may an organisational approach to risk perception. Various criteria, such as cost-effectiveness, choice of comparator, therapeutic benefit, safety, trial design, and timing of submission, have contributed to the non-recommendation of novel medicines. | When compared to the Scottish Medicines Consortium, the Polish HTA's number of unfavourable recommendations is higher (SMC). While lack of cost efficiency was a major factor in negative |
to the corresponding HTA advice issued by the Scottish Medical Consortium (SMC). Recommendations in Scotland, clinical and/or safety concerns predominated in Poland. Whenever AHTAPoL recommended against a treatment, SMC was shown to support that treatment. Scottish HTA methodological guidelines were found to provide greater information on clinical and economic assessments.

| Alam, M. F., Cohen, D., Dunstan, F., Hughes, D., & Routledge, P. (2018). | October 2003 to March 2008 | Wales, England | 23. Patient Access Schemes, Managed Entry Agreement and Risk-Sharing Agreements | To estimate the relationship between changes in prescription co-payments and changes in dispensing rates in Wales during the period October 2003 to March 2008 focusing on those medicines which had the highest number of items dispensed with a co-payment prior to abolition as | The reduction from £6 to £4, £4 to £3, and £3 to £0 was studied over three time periods. Dispensing data from general practitioners in the United Kingdom was analysed monthly using a difference-in-differences model. The model was applied to a subset of 14 medications for which copayments were routinely | The elimination of co-payments in Wales led to an increase in the number of prescriptions filled, although this change in the number of prescriptions filled did not have a major impact. When weighed against findings from earlier research, it appears that the extent of the impact of reduced |

| | | | | | | |
these are the ones most likely to be affected by any changes to co-payments

collected before being eliminated. To separate out the effects of factors other than cost on dispensing in Wales, researchers looked at data from a comparator location (the North East of England) with similar health and socioeconomic characteristics to Wales, and where prescription copayments maintained during the study periods.

copayments is roughly comparable.


Aug 2016

France, Germany, Italy, Spain, and the UK

24. Patient Access Schemes, Managed Entry Agreement and Risk-Sharing Agreements

To gain an understanding of the stakeholder attitudes and experience by undertaking a survey of payers from the major EU markets, and then using the information to derive policy implications for future innovative pricing agreement proposals.

Payer stakeholders were surveyed using an online platform to ascertain the types of innovative agreements already in use, those that are expected to be implemented in the near future, stakeholders' perspectives on these agreements, and the factors that are driving their acceptance. Hospital

Participants in the survey expressed optimism regarding innovative agreements and anticipated a rise in the adoption of such agreements across the EU. However, it is not anticipated that it will adhere to a model that is one size fits all. This is because these agreements need to be adapted to the
Sorenson, C. (2010). To assess the use of CER in verdicts about drug coverage and pricing in six European countries. Researchers found that CER is playing a bigger part in Europe's drug coverage decisions and, to a lesser extent, pricing setting. This not only aids in making decisions based on facts, but it also facilitates the identification of treatments that provide the greatest bang for the buck. According to the results of the study, different nations use different approaches when deciding how to incorporate CER into their medication coverage decisions.
To build on the Appleby et al. work by demonstrating whether it is possible to identify the cost per QALY of marginal services in NHS Scotland. The second aim of this paper is to explore how the NHS makes spending verdicts at the margin and the extent to which cost per QALY evidence informs the decision-making process. Using responses from NHS Boards to the Scottish Government’s 2012/13 Budget Scrutiny and information gleaned from interviews with Finance Directors, we were able to determine which services were on the verge of being cut. Evidence of marginal services’ cost-effectiveness was sought by searching the literature. There was no way to get a good estimate of the threshold due to the enormous variation in cost-effectiveness estimates of marginal services. It’s not surprising, considering that other variables outside cost-effectiveness evidence tend to dominate budgetary decisions. Our findings emphasise the divergent goals of HTA bodies and local decision makers in the health care system. Additionally, the study shows that without extensive investment in health economics resources, it would be exceedingly difficult to make use of cost-effectiveness findings at the local level.

| Pauwels, K., Huys, I., Vogler, | 2008 and 2015 | Belgium, The Netherlands, Patient Access Schemes, Managed | To conduct a comparative analysis | Between September 2015 and June 2016, A number of EU member states have |
S., Casteels, M., & Simoens, S. (2017). Entry Agreement and Risk-Sharing Agreements for oncology medicines between European countries. We conducted a literature search and document analysis to learn more about the laws and procedures around MEA in several EU nations. By compiling data from open sources and the contributions of national health authorities, we have created a summary of the type and substance of MEAs submitted for oncology medications between 2008 and 2015. National health authority representatives involved in the management or negotiation of MEA were interviewed using semi-structured interviews. Adopted MEA differently from one another. It is more frequent to find monetary-based agreements than performance-based ones. Performance-based agreements are not widely used in other EU nations outside Italy. Even in the Netherlands, where such contracts were once common, their use has since been discarded because they conflict with market dynamics. Free stocks and price cuts are common in the English market. Both the Netherlands and Sweden place a premium on research that can be proven to be effective. Belgium uses a combination of the English, Swedish, and Dutch methods. As a common policy instrument, MEA is used by payers in EU.
<p>| Varnava, A., Bracchi, R., Samuels, K., Hughes, D. A., &amp; Routledge, P. A. (2018). | Between October 2010 and September 2015. | Wales, England and Scotland | 27. Health Technology Assessment (HTA) | To assess the medicines appraisal process in Wales, its timeliness and its impact on medicines availability in Wales, and compare its processes and recommendations with the two other UK health technology appraisal bodies (NICE) and the Scottish Medicines Consortium (SMC). | Analysis was performed on all AWMSG drug reviews published between October 2010 and September 2015. The AWMSG procedure and its recommendations were compared to those of NICE and SMC, both in terms of time and quality. In this analysis, we only analysed information that was freely available online. | It has been noted that Welsh patients have access to innovative drugs at a faster rate than their English counterparts. If available, the All Wales Medicines Strategy Group (AWMSG) will adhere to recommendations made by the National Institute for Health and Care Excellence (NICE). However, AWMSG evaluates drugs for which NICE guidelines is not yet available; its conclusions are superseded if and when NICE guidance is published. Conclusions from different HTA bodies in the UK are found to be relatively consistent overall. |</p>
<table>
<thead>
<tr>
<th>Chabot, I., &amp; Rocchi, A. (2014).</th>
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<tr>
<td>January 1, 2002 to June 1, 2013.</td>
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<td>England and Canada</td>
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<td>28. Health Technology Assessment (HTA)</td>
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<td>To review and compare the recommendations of two Canadian agencies alongside an international comparator—NICE in the UK—with respect to their recommendations and the influence of clinical and cost-effectiveness evidence on the recommendations.</td>
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<td>From January 1, 2002, to June 1, 2013, recommendations were compiled from each of the three agencies. Only metastatic or advanced cases of the five most common types of cancer (lung, breast, colon, kidney, and blood) were considered for recommendations. Positive suggestions and the factors that contribute to them are the focus of descriptive studies. Only data that was available to the public and hosted on the agency’s website was considered for each recommendation.</td>
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| Positive recommendation rates vary widely between studies, from 48% for NICE to 95% for Canada’s national approach. A low level of consensus was observed between agencies when making HTA recommendations. In several circumstances, progression-free survival data was considered sufficient rather than overall survival data. After the HTA process, different methods were adopted in each jurisdiction to address cost-effectiveness. NICE would likely make a negative recommendation under these circumstances, but the Canadian approach would likely offer a favourable
<table>
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<tr>
<th>Author(s)</th>
<th>Study Period</th>
<th>Countries</th>
<th>Objective</th>
<th>Methodology</th>
<th>Recommendation</th>
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<tr>
<td>Detiček, A., Locatelli, I., &amp; Kos, M. (2018).</td>
<td>January 2005 – December 2014</td>
<td>Austria, Belgium, Bulgaria, Croatia, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, and UK.</td>
<td>To estimate patient access to orphan and non-orphan medicines for rare diseases in 22 European countries during 2005 to 2014.</td>
<td>The IMS MIDAS Quarterly Sales Data, January 2005-December 2014, was scoured for treatments for rare diseases on the Orphanet list that have been approved during that time period (IQVIA, Danbury, CT). The number of drugs, the median duration to continuous usage, and the cost of medicines were calculated for each country. If continuous sales were recorded during a 12-month window, the drug was regarded to be commercially available.</td>
<td>High costs, limited efficacy/safety evidence, and low societal benefit contribute to a patchwork of access to medicines for patients with uncommon diseases across Europe. The biggest spending on medicines for uncommon diseases is found in Germany, Switzerland, and France. Patients with rare diseases have easier and faster access to treatment options in the United Kingdom, Germany, Switzerland, France, and the Nordic nations.</td>
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<tr>
<td>Morgan, S. G., Vogler, S., &amp; Wagner, A. K. (2017).</td>
<td>August 16th, 2016 to September 23rd, 2016.</td>
<td>Australia, Austria, Canada, England, Germany, New Zealand, Norway, Scotland, Sweden, Netherlands, and USA</td>
<td>30. Patient Access Schemes, Managed Entry Agreement and Risk-Sharing Agreements</td>
<td>To document international experiences with confidential price discounts among public or statutory payers in a sample of high-income countries in North America, Europe, and Australasia.</td>
<td>A private study of community pharmacy customers to gauge their familiarity with and satisfaction with confidential discounts on patented drugs. Multiple types of agreements, including supply contracts, risk-sharing pacts, PASs, MEAs, and others, may be used to negotiate confidential price reductions for patented medications.</td>
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<th>Data Collection</th>
<th>Findings</th>
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<tr>
<td>January 1, 2006 to June 21, 2016</td>
<td>Sweden, United Kingdom, Germany, France, Italy and Netherlands</td>
<td>To review policies of six European HTA agencies on RWD use in REA of medicines</td>
<td>Data about RWD policies at six organisations was gathered through a literature research and interviews with key stakeholders. We looked at 13 policy papers, 9 academic articles, and 6 interviews.</td>
<td>Notably different policies exist regarding RWD usage in REA of drugs. Further, HTA offices have varying policies. Discouragement from using RWD for HTA could result from such variances. A closer harmonisation of policies appears to be required to promote the use of RWD for HTA across Europe. In this regard, recent papers and project ideas of the European network of HTA may serve as a good starting point. Research is needed to see if and how actual RWD use differs from policy intentions.</td>
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<td>Authors</td>
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<td>Countries</td>
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<td>Overall Strategy</td>
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<td>Drummond, M., Jönsson, B., Rütten, F., &amp; Stargardt, T.</td>
<td>2011-2013</td>
<td>Germany, the Netherlands, Sweden and the United Kingdom</td>
<td>To compare and contrast reference pricing with health technology assessment, with a view to identifying the pros and cons of each.</td>
<td>The overall strategy centred on the outcomes of cases involving the initial cost and payment of new drugs. There were four potential locations to choose from. These nations have, at various periods, implemented either policy, sometimes simultaneously. Cholesterol-lowering medications, insulin analogues, rheumatoid arthritis (RA) biologics, and &quot;atypical&quot; antipsychotics were all taken into account.</td>
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<td>Kleijnen, S., Lipska, I., Leonardo Alves, T., Meijboom, K., Elsada, A., Vervolg, V., ... Goettsch, W. G.</td>
<td>Between 2011 and 2013</td>
<td>England, France, Germany, The Netherlands, Poland, and Scotland</td>
<td>To study the role of OS, PFS, and QoL data in REAs informing pricing or reimbursement verdicts in European jurisdictions, by (i) studying whether data on these end points are used, and (ii) examining whether price and reimbursement guidelines and relative effectiveness evaluations (REAs) were compared across a number of nations. At least four national REAs were conducted.</td>
<td>Drug price and reimbursement guidelines and relative effectiveness evaluations (REAs) were compared across a number of nations. At least four national REAs were conducted.</td>
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points are included, and (ii) studying the impact of these data on recommendations. Used to assess the efficacy of anticancer drugs approved for sale in Europe between 2011 and 2013. Totaling 79, these REAs were comprehensive. The guidelines. When possible, data on overall survival is included in all REAs, albeit the quality of this data varies. There is a lack of consistency in the importance of progression-free survival (PFS) between research and HTA committees, and most guidelines provide little to no clarification on the topic. Seventy percent of REAs were found to have PFS information. QoL data were used in 54% of relative effectiveness analyses, however they had a small impact on the HTA decisions. The HTA decision-making process about the relative efficacy of new medicines has been challenged by the fact that regulators in the EU are now admitting

January 2011 until February 2014

England, France and Scotland

34. Health Technology Assessment (HTA)

To evaluate the relevance of indirect comparisons in the German early benefit assessment of new medicines and other HTA processes in England, France and Scotland

From 2011 January to 2014 February, IQWiG evaluated submissions of indirect comparisons. To begin, all German submissions were evaluated to determine which new drugs were introduced over the specified time period and which submissions included indirect comparisons. Second, we identified the mechanism used for every indirect comparison. Third, we looked at the IQWiG decisions about whether or not the indirect comparison was accepted, and we divided the reasons for rejection into some degree of uncertainty in clinical evidence.

This research, which aimed to determine the value of indirect comparisons in the early benefit assessment of new medicines in Germany and other HTA processes in the United Kingdom, France, and Scotland, found that doing so was difficult. Indirect comparisons in the pharmaceutical business are difficult to conduct because of strict regulations.
formal and methodological flaws. Three European nations were selected because they have an HTA-process that is both similar to Germany’s and well-established, and because they provide at least some of the transparency necessary for a fair comparison to be made.

| Vegter, S., Rozenbaum, M. H., Postema, R., Tolley, K., & Postma, M. J. (2010). | May-09 | Scotland and the Netherlands | Health Technology Assessment (HTA) | To identify differences in the outcomes of the recommendations for orphan medicines for rare diseases between 2 European countries: Scotland and the Netherlands. | From their websites, we combed through all orphan medication reports submitted to the Dutch Committee for Pharmaceutical Assistance (CFH) and all orphan medicines guidelines published by the Scottish Medicines Consortium (SMC) up through May of 2009. A drug's indication, the results of the pharmacoeconomic evaluation, the recommendation, and the specific date were collected from | In comparison to Scotland, where just 21% of orphan medication reimbursement requests were accepted, the approval rate in the Netherlands was far higher at 95%. More than half of the Scottish proposals (24 of 37) included cost-effectiveness or cost-utility evaluations, while only one of the Dutch submissions (out of 38) did. |
| Bourke, S. M., Plumpton, C. O., & Hughes, D. A. (2018). | 2014–2016. | UK | 36. Health Technology Assessment (HTA) | Person Trade-Off and Discrete Choice Experiment Methods | Three thousand nine hundred and fifty persons chosen to be representative of the UK general population participated in a person trade-off (PTO) and a discrete choice experiment (DCE). Patients with uncommon diseases, their family members, healthcare providers, and policymakers were surveyed to inform the experimental design. Estimates of public opinion were made on the NHS's prioritisation of the treatment of a common ailment, the lengthening of waiting lists, and the filling of open positions. According to the results of this research, the public does not place a high value on funding suggestions for orphan medications at the higher threshold of cost effectiveness. This research raises questions about the wisdom of the present policies that recommend the orphan medications at a very high threshold, especially in light of the increasing prevalence of these diseases and the high price tag associated with their treatment. | To assess whether there is a UK societal preference to support current NHS policies that permit funding of non-cost effective treatments for rare diseases. It further tested whether a sample of recently approved orphan medicines would be recommended on the basis of societal preference. | reimbursement recommendations and drug use guidelines in the Netherlands and Scotland, respectively. |
| Rosenberg-Yunger, Z. R. S., Thorsteinsdóttir, H., Daar, A. S., & Martin, D. K. (2012). | Canada, Israel, England and Wales, Australia, and the USA | Stakeholders involvement/ views on Reimbursement Process | To review stakeholder involvement of drug reimbursement committee members, patient groups, and industry representatives in the priority setting and appeals processes of six medicines across five drug reimbursement recommendation committees in Canada, Israel, England and Wales, Australia, and the USA. | Qualitative case studies | Case studies of the qualitative nature examine the processes by which five separate drug advisory committees in Canada, Israel, the United Kingdom, Australia, and the United States came to their financing decisions for six pricy medications. Committee members, patient groups, and officials from the industry were interviewed for a total of 48 sources of information. | This research showed that health professionals, academics, and the general public were the most active participants in the process. Some panels had more industry representatives than others. All analysed countries, besides Israel and the United States, allowed pharmaceutical corporations to formally appeal convictions. The sorts of stakeholders, the extent to which they are involved in the overall evaluation, and the procedures for making changes and |
| Cavazza, M., & Jommi, C. (2012). | 1999–2011 | France, Spain, England and Wales, Germany, Sweden, and The Netherlands | 37. Stakeholders involvement/ views on Reimbursement Process | To investigate stakeholder involvement by HTA Organisations (HTAOs) in 7 EU countries and to study whether this involvement depends on (i) the administrative tradition and the relevant conception of the relationship between state and society (contractarian and corporative vs. organic), (ii) the general structure of the healthcare system. For getting information, interviews based on semi-structured questionnaires were used. The interviews were done with 16 important people in the HTAOs in question. A review of the research on HTAOs and interested parties from 1999 to 2011 using PubMed, Ebsco, JSTOR, and Wiley Science. | The study shows that the NICE includes all relevant parties in an HTA process and the following judgement making process. In all UK evaluations, business has the opportunity to vote. The decision-making process is inclusive of all relevant parties, which is typical of the British administrative model. The findings of this research suggest that stakeholder engagement is crucial in the process. | filing appeals all differ. The research uncovered multiple existing involved stakeholders, as well as potential ones. The participation of all important stakeholders was seen to be necessary for a fair and genuine procedure to be developed for the reimbursement of new drugs. |
system and (iii) the role of HTA and HTAOs in the HCS.

strategies developed in one nation may have difficulty being adopted in another due to differences in administrative approaches and healthcare system priorities.

<p>| Grimm, S. E., Strong, M., Brennan, A., &amp; Wailoo, A. J. (2017). | UK | 38. Patient Access Schemes, Managed Entry Agreement and Risk-Sharing Agreements | To develop methods for quantifying risk associated with specific MEAs and for clearly communicating this to decision makers. | Case Studies | We made a &quot;HTA risk analysis chart&quot; that shows the payer strategy and uncertainty burden (P-SUB) as a way to measure the overall risk. The P-SUB is made up of the payer uncertainty burden (PUB), which is the risk that comes from not knowing which technology in the relevant set is the best, and the payer strategy burden (PSB), which is the risk that comes from approving a technology that is not likely to be the best. We show how the method works with the help of three recent technology | To evaluate the risk involved with HTA suggestions, a chart was created to review the payer strategy and uncertainty burden (P-SUB). There is a standardised notion presented to demonstrate the necessity for and possible usefulness of various MEAs, which aids those with decision-making authority in identifying those scenarios. If implemented, HTA has the potential to ensure that MEAs are routinely, consistently, and openly considered. It is expected to be |
| Ferrario, A. (2018). | 2000 and 2014. | Belgium, Estonia, Scotland, and Sweden | 39. Access to Medicines | To assess time to entry of cancer medicines that obtained centralized EU authorization between 2000 and 2014 in a selection of medium-sized European markets was analyzed to address the following objectives. First, to quantify the median time from EU-wide approval to first use (launch) for a sample of cancer medicine and the number of launches in the study countries as of June 2015 and to assess whether longer times to launch and lack of launches affected medicines with high or low expected benefits. Using a complementary log-log model, the correlation between time to launch and a set of variables thought to affect launch was tested for 46 cancer medicines that got EU-wide marketing authorization between 2000 and 2014. The study found that the probability of early access to medicines increased with shorter time intervals from authorization to submission for reimbursement, the presence of a local sales representative of manufacturer, prelaunch evidence of added clinical value, and the short time gap since EU-wide marketing authorization. Manufacturer-government agency communication at an early stage may aid in the identification of medicines with the greatest potential for positive outcomes. | reviews from the UK’s National Institute for Health and Clinical Excellence (NICE). Each of these reviews looked at a price-based MEA. useful for both payers and the industry in the dynamic new pharma landscape. |</p>
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Country/Region</th>
<th>Methodology</th>
<th>Research Design</th>
<th>Findings</th>
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<tr>
<td>Angelis, A., Lange, A., &amp; Kanavos, P. (2018)</td>
<td>France, Germany, England, Sweden, Italy, Netherlands, Poland and Spain</td>
<td>Health Technology Assessment (HTA)</td>
<td>Mixed Methods Study</td>
<td>The research shows that similar standards are applied to studies of different nations. However, the criteria and endpoints that are applied, the requisite degree of proof, and the manner in which they are integrated, all vary across nations, and their relative value is typically unknown. Heterogeneity in HTA recommendations and decision-making may be explained by the incorporation of additional 'social value judgements' beyond clinical and economic evaluation. Greater transparency.</td>
</tr>
</tbody>
</table>

New drug introductions typically take longer in countries with smaller markets, such as Estonia.
feedback from national experts were used to confirm and update the information found in the literature. in the selection of evaluation criteria, the importance and the intensity of their use, could lead to more evidence-based decision-making, which in turn could increase resource allocation efficiency and public confidence and fairness.


To explore whether real-world data (RWD) is incorporated in health technology assessment (HTA) of melanoma medicines by European HTA agencies, as well as differences in RWD use between agencies and across time.

HTA reports published between January 1, 2011, and December 31, 2016, were found on the websites of five agencies: NICE in England, Scottish Medicines Consortium (SMC) in Scotland, Haute Autorité de Santé in France, Institute for Quality and Efficacy in Healthcare in Germany, and Zorginstituut Nederland in the Netherlands. For both REAs and CEAs, information on RWD inclusion was gathered using a

The five agencies' approaches to using RWD in REAs varied, with some stating it simply for prevalence and/or incidence and others citing it for therapeutic efficacy and safety. However, because of variances in practise between agencies and the variable quantities of reports published each year, these results should be evaluated with caution, even if no discernible trend in overall RWD inclusion over time was found. The
| Comanor, W. S., Schweitzer, S. O., Riddle, J. M., & Schoenberg, F. (2018). | US and UK | 42. Pricing | To study the pricing implications of alternate regimes. | In the empirical analysis, the proposition was tested by comparing the prices of the same medicines when they first came out to the prices of the same medicines that had already been on the market in the two countries. In this study, only medicines that have been approved by both the US FDA and the European Medicines Agency for use in the US and the UK and by NICE as being cost-effective in | Even both regulatory and market forces both contribute to value-based pricing in the United Kingdom and the United States, it is not possible to definitively state that these factors have different effects. | optimum setting for RWD application in HTA practice is within CRSs adopted by various HTA agencies, and future research should strive to investigate RWD inclusion and appraisal within these systems across a variety of disease categories. | standard form for data extraction. |
Charokopou, M., Majer, I. M., Raad, J. De, Broekhuizen, S., Postma, M., & Heeg, B. (2015). 2006-2013 Scotland 43. Health Technology Assessment (HTA) To investigate the weight that different pieces of evidence, submitted to the SMC for reimbursement assessment, have on the final recommendation decision by the SMC. A database of SMC submissions from 2006 to 2013 was made. It includes clinical, economic, and other factors taken from published health technology assessment reports. The decision to "accept for use" or "not recommend" a technology was used as the outcome variable. With the help of odds ratios (ORs), both univariate and multivariate analyses were done to figure out how the submitted evidence affected the recommendation decision. While this study found that cost effectiveness analyses are a major consideration in Scottish Medicine Consortium reimbursement recommendations, it found that in other countries (England and Wales), the most influential factors on HTA recommendations were the number of randomised clinical trials, the inclusion of a cost-utility analysis in the submission, the incremental cost-effectiveness ratio (ICER), and whether the product has a...
| Barbieri, M., Hawkins, N., & Sculpher, M. (2009). | 1999 and 2005 England, Scotland | 44. Health Technology Assessment (HTA) | To review the requirements of economic evaluation to support decision-making and considers the extent to which each type of assessment is likely to meet these requirements. It also attempts to address whether the two forms of assessment differ in their impact on decision-making using a comparison of the verdicts made by NICE (under its multiple-technology appraisal system) and the Scottish Medicines Consortium (SMC), which relies on manufacturer assessment. | Between 1999 and 2005, the NICE in the UK used both third-party assessments and assessments done by the manufacturers. After this, some technologies were put into a programme called Single Technology Appraisal, which used an assessment based on the manufacturer. In this part, the role of third-party evaluation in this way of making decisions is looked at. The article looks at what economic evaluation needs to do to help people make decisions and how well each type of evaluation is likely to Only a subset of drugs under consideration by both groups will be compared here. NICE recommendations are stricter than those of the Scottish Medicine Consortium (SMC). The SMC evaluates all novel pharmaceuticals, while the NICE evaluates only a subset of such products. While the Scottish Medicines Consortium relies on manufacturer submissions alone, NICE incorporates both manufacturer and third-party analyses into their recommendations. |
| Nicod, E. (2017). | December 2012 | England, Scotland, Sweden and France | To investigate the drivers of HTA recommendations for a sample of 10 orphan medicines in four countries and identify the reasons for cross-country differences. | A mixed methods research design | HTA recommendations for ten orphan medicines evaluated in England (NICE), Scotland (SMC), Sweden (TLV), and France (HAS) (N = 35) were compared using a validated methodological framework that breaks down these complex decision processes into stages to make them easier to understand, analyse, and compare. These stages were: (1) the clinical/cost- | Results showed that HTA recommendations varied by 60% across nations for the same drugs. Variability in evidence evaluated, as well as varied techniques to addressing ambiguity related to cost effectiveness or clinical efficacy, account for these variations in HTA recommendations. | There are benefits to using a third party for assessment, but doing so may increase costs and lengthen the process. |
effectiveness evidence, (2) its interpretation (for example, as part of the deliberation process), and (3) its influence on the final decision. This made it possible to find both the qualitative and quantitative factors that led to the recommendations, as well as differences between countries. 

The final decisions were also affected by the fact that different agencies use different methods for making HTA recommendations (clinical versus cost-effectiveness), especially when it comes to orphan drugs.

This study improves our understanding of decision processes and the reasons countries reach judgements, despite the constraints of secondary sources of data, the availability of restricted evidence, and the small sample size. It also aids in the identification of non-clinical and non-cost-effective HTA elements that influenced the final decision.
### Appendix 3: Supplementary Material—Quality Assessment Table

<table>
<thead>
<tr>
<th>Study</th>
<th>Organisational characteristics (e.g HTA/NHS)</th>
<th>Data source (database/questionnaire)</th>
<th>Intervention description (MEA/HTA)</th>
<th>Comparability (UK&amp;EU/Dugs)</th>
<th>Assessment of outcome (QALY/preferences)</th>
<th>Data presentation (%/N/Median)</th>
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Appendix 4 - European Medicines Agency (EMA) approved list of innovative medicines licensed in 2017.
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<th>#</th>
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<th>Therapeutic area</th>
<th>Human pharmacotherapeutic group</th>
<th>Active substance</th>
<th>ATC code</th>
<th>Conditional approval</th>
<th>Exceptional circumstances</th>
<th>Accelerated assessment</th>
<th>Orphan medicine</th>
<th>Marketing authorisation date</th>
<th>Marketing authorisation holder/company name</th>
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<td>Cystinosis</td>
<td>Ophthalmologicals, mercaptamine</td>
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<td>21</td>
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<td>no</td>
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Appendix 5: Communication to identify and select expert for interview.

Dear Sir/Madam,

I am contacting you to inquire about appropriate contact in your organization’s Market Access and reimbursement Department, to attend an interview to support a project of Department of Pharmacy, University of Huddersfield, Queensgate, HD1 3DH, Huddersfield, United Kingdom.

The research project is intended to provide the research focus for a module which forms part of PhD degree. This project will evaluate access to medicine situation in UK by reviewing the licensing & health technology assessment recommendations including overall reimbursement processes for sample of innovative medicines in England, Scotland, Wales and in the Northern Ireland. This project has been approved by Research Integrity and Ethics Committee, University of Huddersfield (SAS-SREIC 05.05.20-2).

I am working on this project with Dr. Zaheer-Ud-Din Babar who is Professor in Medicines and Healthcare at Department of Pharmacy, University of Huddersfield. A systematic review of literature on access to medicines in the UK context has already been published in the journal, Research in Social and Administrative Pharmacy (Abbas et al., 2019).

I should be grateful if you could get us connected to an appropriate contact preferably someone working in market access pricing and reimbursement function in your organization. Should you need further information, please don’t hesitate to contact me or my supervisor.

Yours Sincerely,

Nasir Abbas
PhD Student
Department of Pharmacy, University of Huddersfield, Queensgate, HD1 3DH
Huddersfield, United Kingdom
Tel (office): +44 1484471471, 07919537073
Professor Zaheer-Ud-Din Babar BPharm MPharm PhD SFHEA
Professor in Medicines and Healthcare
Director, *Centre for Pharmaceutical Policy and Practice Research*
Department of Pharmacy, University of Huddersfield, Queensgate, HD1 3DH
Huddersfield, United Kingdom
Tel (office): +44 1484471471

z.babar@hud.ac.uk
Appendix 6: Email invitation to identified expert referred by colleague or friend to participate in telephone interview.

Dear Sir/Madam,

I am contacting you as you were identified by your colleague (Name) as appropriate contact in your organization to participate as an expert in a project of Department of Pharmacy, University of Huddersfield, Queensgate, HD1 3DH, Huddersfield, United Kingdom.

The research project is intended to provide the research focus for a module which forms part of PhD degree. This project will evaluate access to medicine situation in UK by reviewing the licensing & health technology assessment recommendations including overall reimbursement processes for sample of innovative medicines in England, Scotland, Wales and in the Northern Ireland. This project has been approved by Research Integrity and Ethics Committee, University of Huddersfield.

I am working on this project with Dr. Zaheer-Ud-Din Babar who is Professor in Medicines and Healthcare at Department of Pharmacy, University of Huddersfield. A systematic review of literature on access to medicines in the UK context has already been published in the journal, Research in Social and Administrative Pharmacy (Abbas et al., 2019).

We would like to invite you to participate in a semi-structured telephone interview in order to further explore about above mentioned project. As a gratitude a book voucher of value £100 would be offered. More information is included in the attached information sheet.

If, after reading the attached information sheet, you would like to participate, please reply to this email and we can arrange a suitable time to call. Should you need further information, please do not hesitate to contact me or my supervisor.

We look forward to hearing from you soon.

Yours Sincerely,

Nasir Abbas

PhD Student
Department of Pharmacy, University of Huddersfield, Queensgate, HD1 3DH
Huddersfield, United Kingdom

Tel (office): +44 1484471471, 07919537073

Nasir.abbas@hud.ac.uk
Professor Zaheer-Ud-Din Babar BPharm MPharm PhD SFHEA
Professor in Medicines and Healthcare
Director, Centre for Pharmaceutical Policy and Practice Research
Department of Pharmacy, University of Huddersfield, Queensgate, HD1 3DH
Huddersfield, United Kingdom
Tel (office): +44 1484471471  z.babar@hud.ac.uk
Appendix 7: Email invitation to identified expert to participate in telephone interview.

Thank you for agreeing to attend the interview to support a PhD study undertaken by me at the Department of Pharmacy, University of Huddersfield, Queensgate, HD1 3DH, Huddersfield, United Kingdom. This project is to evaluate access to medicine situation in the United Kingdom. This project has been approved by the University of Huddersfield’s Research Integrity and Ethics Committee (SAS-SREIC 05.05.20-2).

I am working on this project with Prof Zaheer-Ud-Din Babar who is Professor in Medicines and Healthcare at Department of Pharmacy, University of Huddersfield. A systematic review of literature on access to medicines in the UK context has already been published in Research in Social and Administrative Pharmacy (Abbas et al., 2019). A link of the article is given below.

https://doi.org/10.1016/j.sapharm.2019.12.009

This interview is to further explore about above mentioned project. As a gratitude Amazon voucher of value of £100 would be offered. Please note that the information gathered through this research will remain strictly anonymous and will be reported cumulatively in the thesis. It will not be possible to link back the information to individual participants.

As a reminder, Key objectives of our interview are as below:

To study differences between licensing and health technology assessment recommendations on treatment availability for new innovative medicines in the UK.

To study differences in Health Technology Assessment Recommendation across England, Scotland & Wales.

To assess timelines from licensing to Implementation of HTA recommendations

To assess medicine usage in absence of Health Technology Assessment Recommendation or HTA recommendation as not recommended.

I look forward to speaking to you at agreed interview time.

Yours Sincerely,

Nasir Abbas
PhD Student
Department of Pharmacy, University of Huddersfield, Queensgate, HD1 3DH
Huddersfield, United Kingdom
Tel : +44 7919537073
Nasir.abbas@hud.ac.uk
linkedin.com/in/nasir-a-bba5b1219
Appendix 8: Semi-structured interview guide

Name of Participant:

Department:

Organization:

**Start of interview**

Welcome and introduction

A reminder about the project's history, objectives, and aims

Ask for permission to record the interview on audio.

Make sure privacy is kept (responsible management and storage of data during transcription, analysis, and reporting)

Get permission to take part.

### Question 1 - 11 are to assess timelines from licensing to implementation of HTA recommendations

**First few questions are to talk about the time lag between licensing of new innovative medicines and implementation of HTA recommendations.**

1. What is usually the Sequence to file Health Technology Assessment applications in England, Wales, and Scotland?
   - i. --
   - ii. --
   - iii. --

   **Prompt:** What factors contribute to this preference?
   If we also include EU countries what is sequence of filing do we file first in UK or after EU?

2. Under what circumstances would you prefer to file Health Technology Assessment application in Wales ahead of England?

3. Under what circumstances would you prefer to file Health Technology Assessment application in England ahead of Scotland?

4. Under what circumstances would you prefer to file Health Technology Assessment application in Scotland ahead of England?

5. What are the average timelines to file Health Technology Assessment applications after the approval of the licensing of medicines?

   **Prompt:** can you give us a range (minimum time, maximum time)?
What is Industry average
Variation across drug categories
variations across countries

6. What factors impact HTA submission timelines following licensing of medicines?
   Prompt: for example, Orphan/Non-Orphan, Oncology/non-oncology

7. Do you have any suggestions to reduce average time to file Health Technology Assessment applications after the approval of the license for medicines?
   Are the average timelines increasing or decreasing? What is the trend?
   Do you foresee increase or decrease in average timelines?

8. Are you aware of any challenges after the HTA recommendation are made available, what are the average implementation times to reimburse medicines to patients after the Health Technology Assessment Recommendation is issued?
   England:
   Wales:
   Norther Ireland:
   Scotland:
   Prompt: Industry average/company average- your experience/variability across countries
can you give us a range (minimum time, maximum time)? How often payers base their decisions on the HTA recommendations?
What %age of medicines with a positive HTA recommendation are reimbursed?

9. Are there any instances where HTA positive recommendations have not been implemented or not resulted into positive reimbursement decisions? What has contributed to this situation?

10. Do you have suggestions to reduce overall time from Health Technology Assessment Recommendation to the implementation of HTA recommendation?
    Are the average timelines increasing or decreasing? What is the trend?
    Do you foresee increase or decrease in average timelines?

11. Do you have any suggestions to reduce overall time from License approval to the implementation of HTA recommendation?
    Are the average timelines increasing or decreasing? What is the trend?
    Do you foresee increase or decrease in average timelines?
Question 12-16 are to assess medicine usage in absence of Health Technology Assessment Recommendation or HTA recommendation as not recommended.

12. Are there any instances where medicines were reimbursed despite absence of HTA recommendation?

13. Are there any instances where medicines were reimbursed despite receiving a negative HTA recommendation?

14. In absence of HTA recommendation or negative HTA recommendation what are the key drivers of positive reimbursement decisions?

15. In the absence of HTA recommendation or negative HTA recommendation, what other mechanisms have contributed to improve the patients’ access to medicine in countries across the UK.

   England: 
   Wales: 
   Scotland: 
   Norther Ireland:

16. In what situations HTA submissions are not performed, please provide the reasons for each of the following countries across UK.

   England: 
   Wales: 
   Scotland: 
   Norther Ireland:

Prompt: Do you have suggestions to promote Health Technology Assessment submissions? What is trend? What do you foresee?

Question 17-20 are to study differences in Health Technology Assessment Recommendation across England, Scotland & Wales?

Health Technology Assessment Recommendations are categorized as below:

- Full recommendation/ Positive recommendation
- Negative recommendation
- Restricted recommendation/ Partial Recommendation
- Restrictions linked with managed access programmes or otherwise
17. Do you usually observe differences in Health Technology Assessment Recommendations across England, Scotland & Wales?

18. Are these differences in Health Technology Assessment Recommendation decreasing/increasing over time in Health Technology Assessment Recommendation across England, Scotland & Wales?

19. In future are these differences in Health Technology Assessment Recommendation across England, Scotland & Wales likely to increase/decrease?

20. What are the key drivers of differences in Health Technology Assessment Recommendations across England, Scotland & Wales?

21. Do you have suggestions to reduce this variability over time?

**Question 21 to 24 are to study differences between licensing and Health Technology Assessment Recommendations on treatment availability for new innovative medicines in the UK.**

Few questions about gap between licensing and HTA recommendation in terms of coverage of patient population

22. Is the gap between licensing & HTA decisions increasing or decreasing over time?

23. In recent years have you seen any changes/initiatives in industry practices to reduce this gap?

Prompt: what are those changes/initiatives?

24. Could you think of any other factors/initiatives which may positively or negatively impact the gap between licensing and Health Technology Assessment Recommendations?

Prompt:  
Industry Level  
HTA Bodies Level  
Payers Level  
Patient Level

25. As there are differences between licensing and Health Technology Assessment Recommendations impacting availability of innovative medicines in the UK. How would Brexit impact this situation as now responsibility for licensing of medicines has moved from EMA to MHRA?

Prompt:  
After Brexit what is or what would be expected regarding sequence/order of filing for licensing applications of new innovative medicines to EMA and MHRA?
Are you aware of any enhancements to the UK regulatory or HTA/reimbursement environment?

Do you foresee any impact on access to medicines coverage or time for access to medicines?

Prompt:
Positive impact
Negative impact

**Closing**

26. About access to medicines situation in UK are there any other factors that you think might be important that we have not covered?

27. What are top 3 challenges or barriers for access to medicines situation in UK.

28. Is there anything you would like to add, or ask me?

Thank you very much for participating in the interview. We greatly appreciate your time and input.
Appendix 9: Participant Information Sheet

Department of Pharmacy,
University of Huddersfield,
Queensgate, HD1 3DH
United Kingdom

Participant Information Sheet

Research Project Title: Licensing and Health Technology Assessment Recommendations on treatment availability for new innovative medicines across the United Kingdom

You are being invited to take part in a research project. Before you decide, it is important for you to understand why this research is being done and what it will involve. Please take time to read the following information and discuss it with others if you wish. Ask if there is anything that is not clear or if you would like more information. May I take this opportunity to thank you for taking time to read this.

What is the purpose of the project?

The research project is intended to provide the research focus for a module which forms part of my degree. It will attempt to review the Licensing & HTA recommendations including overall reimbursement processes for sample of innovative medicines in England, Scotland, Wales and in the Northern Ireland.

Why have I been chosen?

This study is reviewing the medicine licensed for company you are working for and we might need some help to find relevant information.
Do I have to take part?

Participation on this study is entirely voluntary, so please do not feel obliged to take part. Refusal will involve no penalty whatsoever and you may withdraw from the study at any stage without giving an explanation to the researcher.

What do I have to do?

You will be invited to take part in interview This should take no more than 30 minutes of your time.

Are there any disadvantages to taking part?

There should be no foreseeable disadvantages to your participation. If you are unhappy or have further questions at any stage in the process, please address your concerns initially to the researcher if this is appropriate. Alternatively, please contact Zaheer-Ud-Din Babar, Professor in Medicines and Healthcare at the School, University of Huddersfield.

Will all my details be kept confidential?

All information which is collected will be strictly confidential and anonymised before the data is presented in any work, in compliance with the Data Protection Act and ethical research guidelines and principles.

What will happen to the results of the research study?

The results of this research will be written up in the PhD Thesis and will be published in any relevant journal. If you would like a copy, please contact the researcher.

What happens to the data collected?

Data will be used to find differences between licensing and Health Technology Assessment Recommendations for new medicines in England, Scotland, Wales and in the Northern Ireland. Study will also quantify the impact of these Health Technology Assessment Recommendations on the patient’s health outcomes.
Will I be paid for participating in the research?
No

Where will the research be conducted?
Department of Pharmacy, University of Huddersfield, Queensgate, HD1 3DH
Huddersfield, United Kingdom

Criminal Records check (if applicable)
Provide a statement declaring that the researcher who may have access to children or vulnerable adults has undergone a satisfactory criminal records check.
Not Applicable

Who has reviewed and approved the study, and who can be contacted for further information?
Zaheer-Ud-Din Babar PhD SFHEA
Professor in Medicines and Healthcare
Department of Pharmacy, University of Huddersfield, Queensgate, HD1 3DH
Huddersfield, United Kingdom
Tel (office): +44 1484471471
z.babar@hud.ac.uk

Name & Contact Details of Researcher: Nasir Abbas
Department of Pharmacy, University of Huddersfield, Queensgate, HD1 3DH
Huddersfield, United Kingdom

Tel (office): +44 1484 471471, 07919537073

Nasir.abbas@hud.ac.uk
Appendix 10: Participant Consent Form

Sample Participant Consent Form

(Required for submission with application for ethical approval)

University of Huddersfield

School

Participant Consent Form (E4)

Title of Research Study: Licensing and Health Technology Assessment Recommendations on treatment availability for new innovative medicines across the United Kingdom

Name of Researcher: Nasir Abbas

Participant Identifier Number:

☐ I confirm that I have read and understood the participant Information sheet related to this research and have had the opportunity to ask questions.

☐ I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason.

☐ I understand that all my responses will be anonymised.

☐ I give permission for members of the research team to have access to my anonymised responses.
I agree to take part in the above study.

Name of Participant: .................................................................

Signature of Participant: ...........................................................

Date: ..............................

Name of Researcher: Nasir Abbas

Signature of Researcher:
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a. 8 cells (100.0%) have expected count less than 5. The minimum expected count is 1.00.

b. The standardized statistic is .000.

### Group * Countries Crosstabulation

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Page | 393
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**Chi-Square Tests**

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<th>Exact Sig. (2-sided)</th>
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**Group * Countries Crosstabulation**

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</table>

a. 4 cells (50.0%) have expected count less than 5. The minimum expected count is 3.06.

b. The standardized statistic is -2.340.
### Chi-Square Tests

<table>
<thead>
<tr>
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<th>Exact Sig. (2-sided)</th>
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</table>

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 9.35.

b. The standardized statistic is -.470.

### Group * Countries Crosstabulation

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Page | 396
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### Chi-Square Tests

<table>
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</table>
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 6.39.

b. The standardized statistic is -.658.