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Antidiabetic medicines prescribing practices in primary care in Northern England: a mixed-methods study

Sara Ramzan
BSc Pharm MSc Pharm

A thesis submitted to the University of Huddersfield in partial fulfilment of the requirements for the degree of Doctor of Philosophy

The University of Huddersfield

School of Applied Sciences

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Thanks are also due to the clinicians who participated in this research.

External research outputs

Peer reviewed publication(s)

- **Ramzan S,** Timmins P, Hasan SS., & Babar ZU. *Cost analysis of type 2 diabetes mellitus treatment in economically developed countries*. Expert Review Pharmacoeconomics Outcomes Research. 2019;19(1):5–14. doi:10.1080/14737167.2018.1513790
- **Ramzan S,** Timmins P, Hasan SS., & Babar ZU. *Trends in global prescribing of antidiabetic medicines in primary care: A systematic review of literature between 2000-2018.* Primary Care Diabetes. 2019;13(5):409–421. doi:10.1016/j.pcd.2019.05.009

Book chapter(s)

- **Ramzan, S**., Abdul, MA., & Babar, ZU. (2019). *Mixed Methods Research in Pharmacy Practice: Basics and Beyond*. In Babar ZU. (Ed.), Encyclopaedia of Pharmacy Practice and Clinical Pharmacy (1st ed., Vol. 1, pp. 46-52). Elsevier.

Conference abstract(s)

- **Ramzan S.,** Timmins P., & Babar ZU. (2021). Is the National Institute for Health and Care Excellence' type 2 diabetes prescribing guidance consistently used among primary care healthcare professionals? A cross-sectional survey in the North of England. Diabetes UK Conference, April 2021
- **Ramzan S.,** Timmins P., Hasan SS., & Babar ZU. (2018). Evolution of antidiabetic medicines used in the treatment of type 2 diabetes mellitus over the period 2000-2017: A systematic review of the literature. Health Services Research & Pharmacy Practice Conference 2018.

Presentation(s)

- **Ramzan, S.** (2019). Antidiabetics in England: Exploring Prescription Patterns & Health Outcomes. University of Huddersfield 3-minute thesis competition 2019. (*semi finalist*)
- **Ramzan, S.** *(*2018). Systematic reviews: A step-by-step guide for beginners. HUD Pharmacy practice seminars. University of Huddersfield, 4th October 2018.

Other publication(s)

- **Ramzan S.,** Timmins P., Hasan SS., & Babar ZU. (2018). Trends in prescribing of antidiabetic medicines in primary care: a systematic review of the period 2000-2018. PROSPERO 2017 CRD42017074974 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42017074974

Abstract

Antidiabetic medicines are widely used in primary care to prevent, treat and reduce diabetes-related complications. Abundant empirical evidence is available on the management of adults with type 2 diabetes but still much controversy exists about how to prescribe antidiabetic medicines. It is suggested that there are geographical variations in the prescribing of antidiabetic medicines across England, though it is not clear what causes these differences.

The aim of this thesis was to investigate primary care clinicians' antidiabetic medicines prescribing practices in Northern England. First, a systematic literature review was conducted to understand which antidiabetic medicines were being prescribed, then a second systematic literature review was conducted to understand how much was being spent on these medicines. A qualitative study (n=21) provided information about general practitioners' experiences with prescribing antidiabetic medicines. This study also explored factors which influences the general practitioners prescribing choices and referral behaviours. A survey (n=125) expanded on the findings from the qualitative study and provided information on general practitioners, nurses and practice pharmacists preferred stepwise approach to prescribing antidiabetic medicines. Then, a case study surveyed the price of two antidiabetic treatments in a cross-national context.

Variation in antidiabetic medicines prescribing was found to be a common and diverse issue in general practice. The choice of antidiabetic medicines was individualised to the patients based on factors such as notions of the severity of the disease as well as patients' behaviours. The general practitioners described a varying and flexible approach to NICE prescribing guidelines depending on their own ideas and agendas. The interviewees seemed to have varying insight to the clinical practice-evidence gap. The general practitioners' knowledge about NICE guidelines on type 2 diabetes management (NG28) was indirect as the use was filtered through a number of secondary interpretative channels. The general practitioners described varying antidiabetic prescribing practices. Adequate skills and knowledge about antidiabetic medicines seemed more influential than written sources. The challenges in antidiabetic prescribing were diverse but often characterised to be related to tension between competing factors such as advocating for the best care for the patients or keeping prescribing costs down. A conceptual model was developed which summarises the general practitioners' beliefs about antidiabetic medicines which influences their prescribing practices on an individual, local and national level.

The importance of antidiabetic prescribing in primary care seems to be well understood by the general practitioners. The general practitioner's management of adults with type 2 diabetes was in accordance with the NICE guidance. However, the findings suggest that the flexible guidance from NICE has resulted in varying antidiabetic prescribing practices in primary care. There remain areas of uncertainty in antidiabetic prescribing such as in which order to prescribe treatments and how to gain confidence in prescribing the full range of available treatments. Given the complex nature of the challenges in antidiabetic medicines such as suboptimal use of available antidiabetic medicines and varying prescribing guidelines future interventions to optimise prescribing of antidiabetic medicines may need local and national interventions which may require changes in the current prescribing practices in primary care.

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List of abbreviations

ACCORD	The Action to Control Cardiovascular Risk in Diabetes
ADA	American Diabetes Association
ADVANCE	The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BNF	British National Formulary
CCGs	Clinical Commissioning Groups
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
COREQ	32-item consolidated criteria for reporting qualitative studies
CVOTs	Cardiovascular outcomes trials
DAFNE	Dose Adjustment for Normal Eating
DAWN	Diabetes, Attitudes, Wishes and Needs
DAWN2	The second Diabetes Attitudes, Wishes and Needs
DESMOND	Diabetes Education and Self Management for Ongoing and Newly Diagnosed
DPP-4i	Dipeptidyl peptidase-4 inhibitors
EADS	European Association for the Study of Diabetes
EMPA-REG	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 diabetes Mellitus Patients
EU	European Union
GI	Gastrointestinal
GDG	Guideline Development Group
GDPR	General Data Protection Regulation
GLP-1RA	Glucagonlike peptide 1 receptor agonist
GMC	Medical School Council
GPs	General practitioners
GRAMMS	Good Reporting of a Mixed Methods Study
ICD	International Classification of Diseases
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
MHRA	Medicines and Healthcare products Regulatory Agency
NG28	Type 2 diabetes in adults: management
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ORIGIN	Outcome Reduction With Initial Glargine Intervention
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses

PROSPERO	The International Prospective Register of Systematic Reviews
QOF	Quality and Outcomes Framework
SGLT-2i	Sodium-glucose co-transporter 2 inhibitors
SOUL	A Heart Disease Study of Semaglutide in Patients With Type 2 Diabetes
SRIEC	School Research Integrity and Ethics Committee
SUSTAIN	Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes
T2D	Type 2 diabetes
UK	United Kingdom
UKPDS	United Kingdom Prospective Diabetes Study
WHO	World Health Organisation

FOREWORDS

i. Staging this thesis

This PhD thesis revolves around antidiabetic medicines prescribing practices in primary care. Antidiabetic medicines use for type 2 diabetes (T2D) has been constantly changing in the last 20 years. However, despite the increase in availability of antidiabetic medicines treatment outcome among patients are still suboptimal. In this dissertation I argue that there is room for improvement in the prescribing of treatments used to treat adults with T2D in England. This dissertation looks at how primary care clinicians make decisions about which antidiabetic medicines to prescribe for patients with T2D and what influences these prescribing decisions.

When I started my PhD journey, I did not have much knowledge about primary care prescribing. Being a researcher with one leg in community pharmacy and the other leg in academia I believe that pharmacists are experts in medicines. With our clinical knowledge we are able to advice general practitioners (GPs), nurses and other healthcare professionals in how to use medicines. With my PhD research I hope to be able to contribute towards identifying barriers to effective management of T2D in primary care, and thereby contribute to optimisation of prescribing practices in the future.

The review of the literature identified gaps in how primary care clinicians in the United Kingdom (UK) were making prescribing choices when prescribing for patient with T2D and led me to ask a number of pertinent questions. I for example questioned: how do clinicians who treat patients with T2D use the NICE prescribing guideline in their clinical practice, and how do they stay updated with latest clinical guidance? How confident do the clinicians feel in treating patients with T2D? If they are using NICE prescribing guideline in their daily practice, are the recommended treatments sufficient to treat patients effectively? And who is responsible for ensuring that patients receive the best possible care?

In order to explore all these aspects related to T2D prescribing practices in primary care, I have chosen an exploratory mixed-methods research design. I have started with the qualitative component as opposed to the quantitative component in order to take a step back to ask the fundamental questions; who is involved in prescribing, and what do they know about the available treatments? It was my intention to conduct a mixed-methods study which would explore perceptions, attitudes and knowledge which the clinicians recognised and did not recognise to influence them during their daily practice.

ii. About the researcher and her PhD Journey

My first real-life experience with research was in 2012 during my gap year when I was awarded a scholarship for a research year in Clinical Pharmacy at University of Copenhagen in Denmark. After completing my bachelor's degree, I had felt unmotivated to continue my studies, and this experience introduced me to the many reasons which makes medicines use so complex. At that time, I knew I had to continue on this path and involve myself in research which unravelled the barriers to effective communication between patients and doctors. After completing my master's degree, I moved to the United Kingdom (UK) where I started working as a locum pharmacist while applying for PhD scholarships. In July 2017 a dream came true and I was awarded a PhD scholarship by the School of Applied Sciences, University of Huddersfield in the UK.

The initial idea for this project emerged from a discussion between the researcher's two supervisors, Zaheer Babar (ZB) and Peter Timmins (PT), who found that despite much research on management of T2D, clinical inertia was still a challenge in primary care. I chose to build on their idea and conducted a mixed-methods study for two main reasons. Firstly, my previous experience was primarily with qualitative research so this was an opportunity to develop my qualitative research skills further as well as gaining experience with using quantitative research methodology. Secondly, the project had elements of health services research which were within my interest area.

From the first day of embarking on the PhD journey it was exciting, challenging and rewarding, and not one day was the same. Each stage of the research had its own challenges right from writing the research protocol to developing research materials, to recruiting participants for the mixed-methods study, to analysing data and writing up the PhD thesis. My family, supervisors and fellow PhD researchers provided me with emotional support and motivation to push through each of these challenges. Oral presentations such as the University of Huddersfield' 3-minute thesis competition and publication of papers and a book chapter gave me inspiration and motivation to keep learning, growing and moving forward with my research. At the beginning of my third year of PhD our family was extended, and our precious daughter was born. My little girl became my most encouraging research partner throughout the remaining of the PhD journey. Shortly after my maternity leave the global pandemic, COVID-19, was at its first peak. Again, during this time my family, supervisors and fellow PhD researchers gave me the strength and motivation to overcome the challenges of completing the data analysis and writing up my PhD thesis while managing a part-time job in community pharmacy and an energetic toddler.

CHAPTER 1
Introduction

1.1Background

The aim of this review of the literature is to analyse and synthesise scientific literature related to antidiabetic medicines prescribing in primary care. This chapter is a particularly important component in order to summarise existing knowledge, prevent duplication of existing studies and present varying views of the research topic.

1.1.1 Type 2 diabetes

Diabetes is a global health problem (WHO, 2009). Current estimates by the World Health Organization reports 422 million people worldwide to be diagnosed with diabetes (WHO, 2020a). It is estimated that 4.7million people in the United Kingdom (UK) have type 2 diabetes (T2D), this equals one in fifteen people (Diabetes UK, 2019). Between 1998 and 2018 the number of patients diagnosed with diabetes in the UK has more than doubled (Diabetes UK, 2019). This estimate includes a high number of people who are estimated to have T2D without being diagnosed. In 2017/18 the prevalence of T2D in England was estimated to be 6.8% (NHS Digital, 2020b). National statistics shows that the prevalence of T2D is slightly higher among men than women (Diabetes.co.uk, 2019). Early diagnosis is vital as onset of complications can start long before a patient is diagnosed (Diabetes UK, 2019).

T2D is a complex and chronic condition accounting for 9 out of 10 of all diabetes cases (IDF, 2020). The metabolic syndrome is characterised by high blood glucose levels in the body caused by either ineffective use of insulin or inability to produce insulin (Kahn, Cooper, & Del Prato, 2014). Insulin is an essential hormone which is produced by the pancreas. It is responsible for the breakdown of carbohydrates from consumed food and turning it into glucose. As a response to this the pancreas releases insulin. If this mechanism is not working properly, blood sugar levels in the blood stream keep rising and eventually lead to hyperglycaemia. Diabetes is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation. It is estimated that six in ten people do not have any symptoms when they are diagnosed with T2D and one in three will have complications with their eyes, feet, kidneys or nerves by time they are diagnosed (Diabetes UK, 2019). It is known to cause macro- and microvascular damage which has contributed significantly to the already growing healthcare costs associated with T2D (Hex, Bartlett, Wright, Taylor, & Varley, 2012).

1.1.2 Changing landscape of antidiabetic medicines

Drug treatment remains the cornerstone of the clinical management of adults with T2D. To date, insulin therapy is the only drug class which is solely injectable. There are another eight drug classes which are available to treat T2D in England, and these exists as oral and/or self-injectable formulations (table 1.1). Insulin was discovered almost 100 years ago and became available as the first drug to treat T2D (Fralick & Zinman, 2021). During the 1950's sulfonylurea and biguanides (metformin) became available and in the late 1990's and early 2000 alpha-glucosidase inhibitors (acarbose), glinides (repaglinide) and thiazolidinediones were also launched. Since then, a number of newer medicines have been licensed

to treat T2D including Dipeptidyl peptidase-4 inhibitors (DDP-4i), glucagon-like peptide 1 receptor agonists (GLP-1RA) and sodium-glucose co-transporter 2 inhibitors (SGLT-2i).

Table 1.1 Overview of drug classes most frequently used to treat type 2 diabetes in England and their year of introduction.

Year of introduction*	Antidiabetic drug class	Examples of licensed medicines
1922	Insulin	Humalog, NovoRapid, Humulin R, Lantus, Tresiba
1950	Sulfonylurea	Glibenclamide, Gliclazide, Glimepiride
1958	Biguanides	Metformin
1995	Alpha-glucosidase inhibitors	Glucobay, Glyset
1997	Glinides	Nateglinide and Repaglinide
2000	Thiazolidinediones	Pioglitazone
2005	Glucagon-like peptide 1 receptor agonists	Bydureon, Byetta, Victoza, Semaglutide
2006	Dipeptidyl peptidase-4 inhibitors	Sitagliptin, Saxagliptin, Alogliptin, Linagliptin
2013	Sodium-glucose co-transporter 2 inhibitors	Canagliflozin, Dapagliflozin, Empagliflozin

*As per introduction to first territory

For many years HbA1c levels was the driver for treatment of patients with T2D. In 1998 the United Kingdom Prospective Diabetes Study reported long-term metabolic effects of metformin and reduction of cardiovascular risk with use of metformin (UKPDS, 1998a). This led to metformin being promoted to be used as the preferred initial treatment on many national and international T2D guidelines (Diabetes Australia, 2009; Diabetes Canada Clinical Practice Guidelines Expert Committee, 2018; IDF, 2017; Inzucchi et al., 2015; NICE, 2015). Around 2007 Nissen and Wolski (2007) conducted a meta-analysis of published studies which scrutinised the association between rosiglitazone and increased risk of myocardial infarct and death from cardiovascular causes (Nissen & Wolski, 2007). The authors were able to prove serious adverse cardiovascular effects of treatment with rosiglitazone, and this challenged the assumption that primary outcomes of antidiabetic medicines only should be based on HbA1c outcomes. In 2008 the Food and Drug Administration (FDA) updated their guidance for industry, and all new antidiabetic medicines were required to evaluate for cardiovascular risk (FDA, 2008). In the last two decades an increasing number of head-to-head studies which have compared newer antidiabetic medicines with older antidiabetic medicines have been published. There is still no clear data to indicate which drug therapy should be prescribed in preference of other therapies as first, second and third-line treatment.

1.1.3 Economic burden of type 2 diabetes

Long-established treatments such as metformin and sulfonylurea have been on the market for a long time and have become cheaper prescribing options (Bailey, 2017; Sola et al., 2015). Use of newer antidiabetic drug classes have been associated with increased cost of treating patients with T2D (Curtis et al., 2018). In 2015/2016 sulfonylurea cost between £4 and £6 per item prescribed as compared to newer treatments such as DDP-4i and SGLT-2i which cost approximately £40 per item prescribed (Curtis et al., 2018). In the period April 2017 and March 2018 the total cost of items prescribed for diabetes in primary care in England was £53.4 million (NHS Digital, 2018). This accounts for 4.9% of the total number of prescribed items in primary care. In the ten year period between 2007/2008 and 2017/2018 the volume of prescribed items were 22.6 million items prescribed for £421.7 million which increased to 53.4 million items prescribed for £1,012.4 million (NHS Digital, 2018). Statistics published

by NHS Digital shows that the British National Formulary (BNF) subsection 6.1 'Drugs used in diabetes' since 2007/08 has accounted for the highest total net ingredient cost. Currently the drug used in diabetes accounts for £1,012.4 million in total net ingredient cost and make up 11.4% of the total primary care net ingredient cost (NHS Digital, 2018). Although an upward trend in net ingredient cost has been observed, it is important to be aware that costs and price of medicines are unstable due to the way prices are negotiated with manufacturers (Vogler, Zimmermann, Ferrario, Wirtz, & Babar, 2015).

Statistics from OpenPrescribing (figure 1.1) shows that the Northern England (North West Commissioning Region and North East and Yorkshire Commissioning Regions highlighted in figure 1.1) have the highest items for drugs used in diabetes per 1,000 patients in England. Between 2016 and 2020 this trend has fluctuated from 75.4 drugs/ 1,000 patients to 100.48 drugs/1,000 patients (OpenPrescribing.net, 2020).

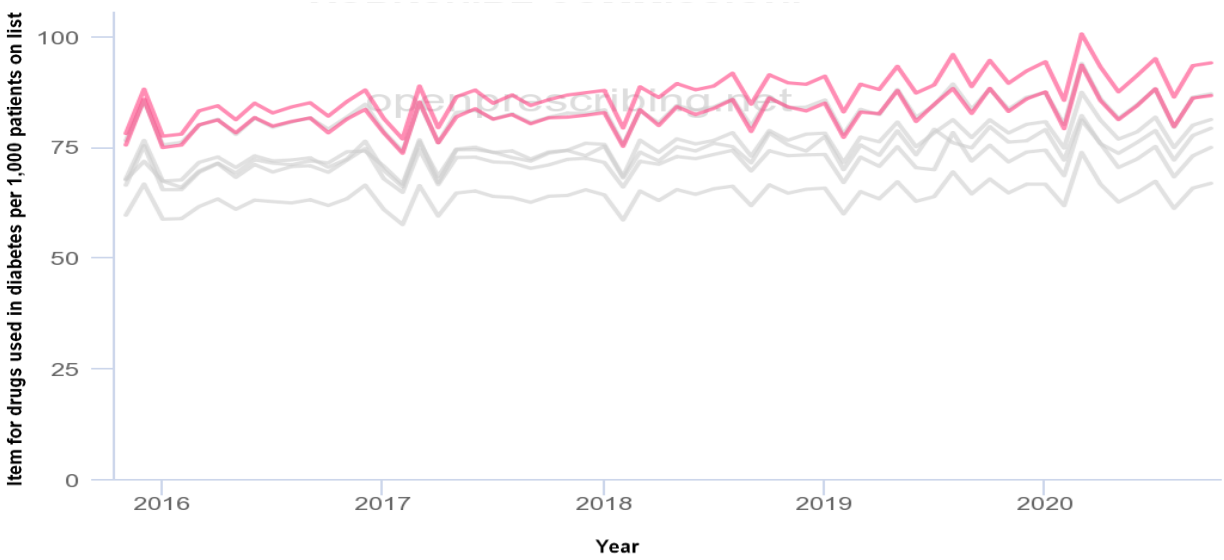


Figure 1.1 Items for drugs used per 1,000 patients in diabetes in England (OpenPrescribing.net, 2020). Northern England (North West Commissioning Region and North East and Yorkshire Commissioning Regions highlighted in red.

1.1.4 Prescribing in primary care

The National Health Service (NHS) is responsible for the majority of health services in England. When a person faces health problems the first point of contact would be primary healthcare (NHS, n.d.-b). The primary healthcare is provided by general practitioners, nurses, practice pharmacists and other healthcare providers such as ophthalmologists and dentists. If the condition cannot be managed in primary care, the healthcare provider has the opportunity to refer the person to other parts of the health system such as secondary care (NHS, n.d.-b).

In England and Wales, the National Institute for Health and Care Excellence (NICE) issues recommendations in various therapeutic areas to provide patients, clinicians and the public with guidance on best practice (NICE, n.d.-d). While it is considered good practice to consult NICE guidance when making prescribing decisions, clinicians do not need to give NICE guidance priority over other guidelines (NICE, 2015). NICE was originally established by the Department of Health in 1999 with an aim to end 'postcode lottery in prescribing' and secure greater cost-effectiveness and consistency in

publicly provided healthcare. This was a measure to reduce area variation in availability of healthcare (Audit Commission, 1994). It has been nationally and internationally recognised for producing guidelines which integrates cost-effectiveness into technology appraisals (Oliver, Mossialos, & Robinson, 2004). NICE guidelines are drawn by Guidelines Development Groups (GDGs) who follow a rigid methodology for producing guidelines (NICE, 2020). The GDGs consist of medical professionals, representatives of patient and care groups and technical experts which represent all interested parties (NICE, n.d.-a). Stakeholder and independent organisations are given two consultation periods to comment on produced draft guidelines. Once the committee has finalised the guidelines it is formally submitted to NICE who approves the guideline and issues the guidance to the NHS (NICE, n.d.-b).

The management of care of patients in primary care is driven by a point system where the general practices are paid for their performance, also known as the Quality and Outcomes Framework (QOF) payments (NHS England, 2018). The introduction of QOF payments have led to standardisation of long-term condition care (NHS England, 2018). QOF provides annual data for general practices, including the number of patients with diabetes (type 1 and type 2) and levels of glycaemic control. While the QOF performance scheme ensures that high quality care is delivered to patients it does not measure the level of personalised care provided by healthcare providers (NHS England, 2018).

The main clinical guidelines used to prescribe for patients with T2D in the UK are:

- 'Type 2 diabetes in adults: management' (NG28) published by NICE, published In 2015 and last updated in 2017 (NICE, 2015).
- 'Pharmacological management of glycaemia control in people with type 2 diabetes' published by Scottish Intercollegiate Guidelines Network (SIGN), published in 2017 (SIGN, 2017).
- 'Management of hyperglycaemia in type 2 diabetes' — a consensus report from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), published in 2018 (Davies et al., 2018).

Prescribing guidelines support clinicians and patients in making appropriate prescribing decisions (Institute of Medicine Committee on Clinical Practice, 1992). Clinical guidelines are defined as "*recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options*'' (Institute of Medicine, 2011). Further, an appropriate prescribing decision must give consideration to the appropriateness, efficacy and tolerability of available treatments (General Medical Council, 2013).

According to the World Health Organization (WHO) "*rational use of medicines requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community*" (WHO, n.d.-b). Given the complex nature of T2D it is important to be aware that prescribing guidelines provide general advice, and patients may require more bespoke prescribing.

Twenty percent of elderly patients over 70 years with T2D suffer from multiple conditions and take five or more medicines (Rollason & Vogt, 2003). A holistic approach to prescribing which considers adverse

drug reaction and/or interactions due to polypharmacy may be necessary (Masnoon, Shakib, Kalisch-Ellett, & Caughey, 2017). Furthermore, the clinicians constantly need to balance the risks and benefits of therapeutic options as more evidence emerges (Drazen, Morrissey, & Curfman, 2007). The risk of nonadherence to prescribed treatment increases as the number of prescribed medicines increases (Gallagher, Barry, & O'Mahony, 2007). Between 10-20% of all adults admissions to the hospital are found to be related to adverse drug reactions (Beijer & de Blaey, 2002). It is estimated that between 2035 and 2045 diabetes-related complications will increase 20-30% above the levels in 2000 (Bagust, Hopkinson, Maslove, & Currie, 2002). Hence, it the study showed that diabetes-related complications and associated healthcare related costs present a serious clinical and financial challenge to the NHS in the UK.

Most routine management of chronic conditions such as T2D occurs in primary care (The King's Fund, 2010). In the period 1997 to 2007 the number of consultations among patients with T2D doubled from 4.2 consultations per year to 8.7 consultations per year (Currie, Gale, & Poole, 2010). A recent report published by the King's Fund on the rising cost of medicines to the NHS showed that the year-on-year increase in prescribing cost was less in primary care (0.6% per year between 2010/2011 and 2016/2017) as compared to hospitals (12.1% per year between 2010/2011 and 2016/2017) (The King's Fund, 2018). It is estimated that 5% all prescriptions written by GPs are for diabetes (Stedman et al., 2019).

Safe and effective prescribing should be a core competency of all doctors (Committee, 1993). The Medical School Council's (GMC) Safe Prescribing Working Group has identified eight competencies in relation to knowledge and skills in prescribing required by all foundation doctors (Group, 2008). Further, the GMC has formulated criteria for good practice in prescribing which includes (General Medical Council, 2013):

- Effective treatment based on the best available evidence.
- Selection of appropriate therapies which serves the patient's needs.
- Appropriate review of dosage and side-effects.
- Stopping treatment when it is not effective.
- Understanding advantages and disadvantages of any treatment.

1.1.5 Focus of this literature review

In the previous sections the increasing burden of T2D on the NHS was highlighted. The next sections of this review seek to cover the following aspects of management of adults with T2D in primary care:

1) To obtain an overview of current management of adults with T2D in primary care in England.
2) To identify what influences primary care GPs' prescribing decisions.
3) To gather evidence which could inform the development of current PhD research.

A Venn diagram (figure 1.2) was drawn to identify topics relevant to antidiabetic medicines prescribing practices in the primary care setting. The intersection of the three circles presents the focus of this PhD thesis. First general studies on influences on GPs' prescribing behaviours and use of prescribing

guidelines in primary care have been described. This is followed by evidence-based studies on the current state of T2D management in England. Then, the guidance from NICE on prescribing for patients with T2D (NG28) have been introduced along with diabetes practitioners' concerns regarding NG28. This is followed by a rationale for the thesis, aims and objectives for the mixed-methods study and an outline of the thesis chapters.

During the literature review conducted in Pubmed, Medline, Springer Link, Scopus and Science Direct were searched for relevant papers between 1990 and 2021. The following search terms were used during the literature review: Clinical inertia, therapeutic inertia, diagnostic inertia, diabetes, type 2 diabetes, diabetes mellitus, type 2 diabetes mellitus, glucose lowering medicines, glyceamic control, early medical intervention, delay in treatment, diabetes complications, cost-effectiveness, prescribing guidelines, NICE and NG28. This literature presented in this chapter does not seek to be comprehensive of all available literature but rather introduce topics and research papers which are relevant to understand and discuss the research questions posed in section 1.5. The presented literature focus on outcomes in England, however when the findings are for the UK this has explicitly been stated. It is not within the scope of this study to assess whether the recommendations in local, national and international prescribing guidelines are justified with sufficient scientific evidence. Multiple definitions of clinical inertia are described in the literature. The definition adapted in this PhD thesis is defined as "*lack of treatment intensification in a patient not at evidence-based glycemic goals for care*" (Giugliano, Maiorino, Bellastella, & Esposito, 2019).

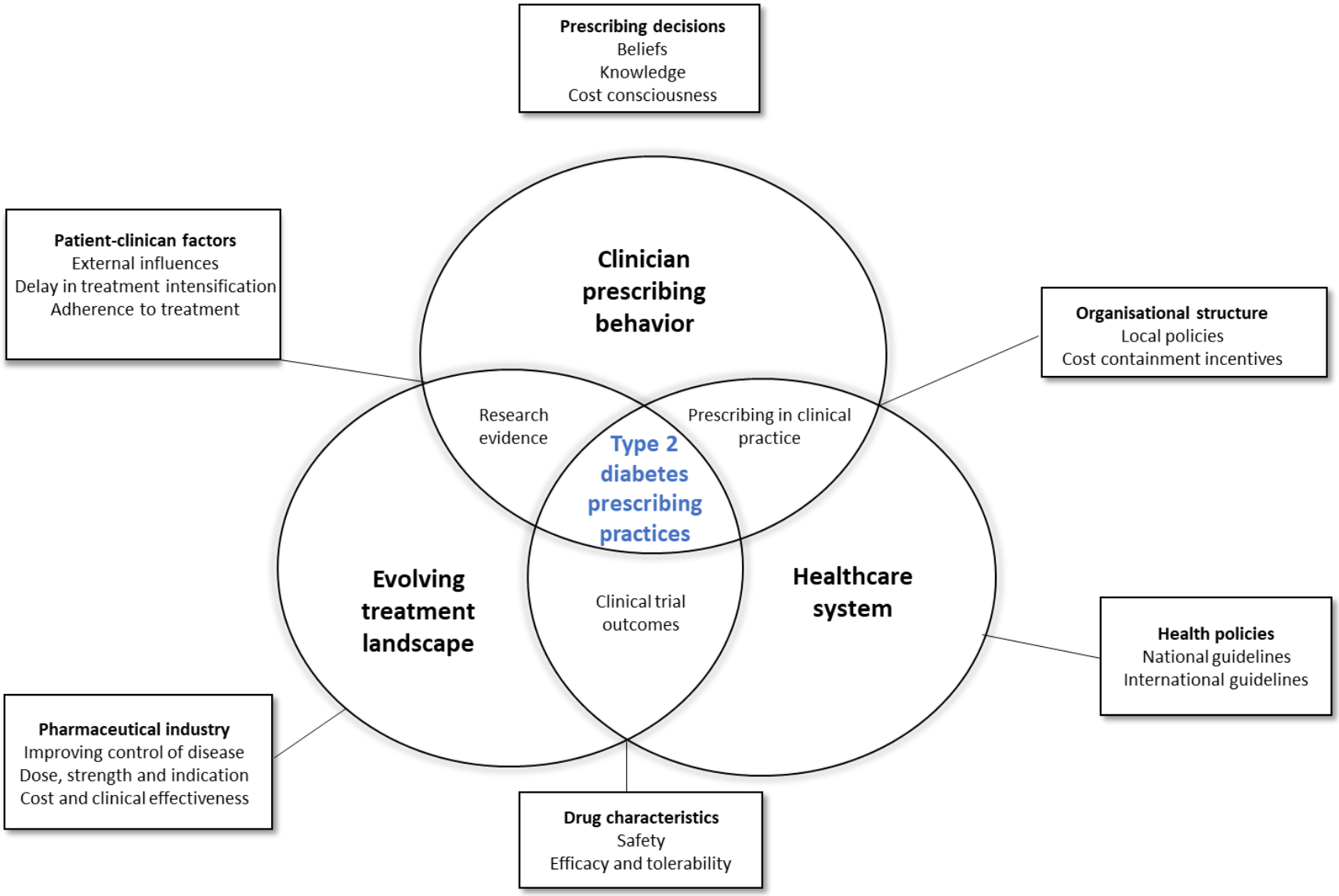


Figure 1.2 Venn diagram of topics relevant to this PhD thesis.

1.2 General practitioners' prescribing behaviours

The study conducted by Jones et al. compared the prescribing of new drugs between GPs and consultants in a teaching hospital, nearby general hospital and general practices in Birmingham (Jones, Greenfield, & Bradley, 2001). The study showed that GPs prescribed new drugs for a wide range of clinical conditions as compared to consultants who prescribed within their speciality area. The study was carried out over a two-year period during which the GPs prescribed between five and seven new drugs. The launch of the new drug classes was received positively by consultants and GPs. The GPs willingness to prescribe a new drug was found to be dependent on the perceived risk and availability of alternative treatments. Prescribing a new drug was seen as an opportunity to reduce the cost of existing treatment but also as an alternative treatment for patients where existing regimen was unsatisfactory. Consultants were more willing to try a new drug if existing treatment was not appropriate (e.g., effectiveness, tolerability) for a patient. In this study GPs reported that seeing a drug prescribed by a consultant made it acceptable to prescribe. Other approaches to prescribing by GPs was a 'trial and error' approach where they would prescribe the drug to a patient and stop using it for future patients if it was not effective or the patients experienced undesirable side-effects. Consultants and GPs found pharmaceutical representatives to be an important source of information. The consultants would often know about a new drug before it was launched. Consultants described themselves to have a good relationship with pharmaceutical representatives and found them particularly useful for keeping them updated with launch of new drugs. They would ask the pharmaceutical representatives to provide them with scientific literature on new drugs. Other sources of information which they mentioned were drug marketing, scientific meetings and literature. GPs on the other hand, had no prior knowledge about launch of new drugs. They heard about new drugs from various places and were not always sure where. The only information they would get about new drugs from the pharmaceutical representatives were the drug company materials.

Jacoby et al. interviewed 56 GPs who were low, medium and high volume prescribers of eight new drugs in Northern and Yorkshire Health Authority Region, England (Jacoby, Smith, & Eccles, 2003). This study showed three main influences on their prescribing of new drugs: internal influences (risk aversion, confidence, experience in prescribing area, and cost-consciousness), external influences (e.g. peers, other prescribers, literature prescribing guidelines and drug companies) and drug characteristics (efficacy, safety, tolerability and cost). Additionally, it was shown that low prescribers more often demonstrated conformism and cost-consciousness as compared to high prescribing GPs.

Prosser et al. explored the differences in prescribing between 107 GPs in low and high volume prescribing practices in two health authorities in the North West of England (Prosser & Walley, 2003). Both groups of prescribers identified themselves as cautious and conservative in their prescribing approach. Balancing the cost and effectiveness of new drugs was considered important. However, this was not described as a limitation to prescribing effective high cost drugs to patients where cheaper alternatives were not tolerated or were ineffective. They recognised cost pressures on the healthcare system and hence did not find it sustainable to prescribe high cost medicines for all patients. High volume prescribers were happy to trial new drugs in their own practice, while low volume prescribers

were more cautious and waited with prescribing new drugs until they had seen the safety established through prescribing from high volume prescribers or hospital consultants. In this study, consultants' endorsement of a new drug was a major influence on the GPs decision to prescribe a new drug. Failure of optimal treatment with first-line treatment was often mentioned as reason for trying new drugs. In the study conducted by Prosser and Walley (2003) both low and high prescribing GPs stated that they had concerns about information from the pharmaceutical industry. Nevertheless, high prescribing GPs found that they were able to form their own opinion based on the promotional materials they were provided.

Another paper published by Prosser et al. reported on influences on GPs' decisions to prescribe a new drug (Prosser, Almond, & Walley, 2003). The participants were recruited from low, medium and high volume prescribing practices in two health authorities in North West of England. The study found that GPs rarely actively sought for information and were opportunistic recipients of new drug information. Further, the GPs' decision to initiate a new drug was to be influenced by 'who says what'. They found that 49% of the GPs would gather information about new drugs from pharmaceutical industry (advertising, promotional literature, representatives and sponsored meetings). Their decision to prescribe a drug would be influenced by local prescribing guidelines and hospital consultants.

Carthy et al. performed a qualitative study which investigated the cost and variation in prescribing among 17 GPs in England (Carthy, Harvey, Brawn, & Watkins, 2000). The GPs identified themselves as cautious prescribers but had variable attitudes to using prescribing support tools such as the BNF and prescribing software. In this study community pharmacists were recognised for their role in identifying prescription errors but the GPs hardly recognised the pharmacists' potential role in terms of providing decision support. This study also echoed findings regarding GPs' decision-making described in the above-mentioned studies. Additionally, the authors also carried out a quantitative survey with 1,714 GPs (Watkins et al., 2003). The study found that the prescribers who were prescribing costly medicines were significantly more likely to see drug company representatives and to prescribe newly available drugs. Further, they would feel uncomfortable with concluding a consultation with advice only and were also more likely to issue a prescription to patients who expected to get one.

Prosser and Walley et al. explored cost-consciousness in prescribing in England (Prosser & Walley, 2005). The study was a combination of focus groups and interviews with GPs and primary care organisation stakeholders. GPs found cost to be secondary to effectiveness and safety of the prescribed drugs. Although cost was considered to be important, cost considerations varied among the GPs. A small number of GPs reported that they rarely considered the cost of the prescribed medicines. Their first consideration was to quality of prescribing; they found that considering the cost of the medicine would undermine the quality of prescribing and the approach was inconsistent with providing patient-centred care. Their second consideration was practical as they found they were restricted by time constraints. However, there was a general consensus among the GPs that there is growing cost-awareness in GPs. The GPs reported to have access to drug prices through computerized decision-support systems and paper sources such as the British National Formulary (BNF). Although there was a general consensus that GPs lacked knowledge about *actual* cost of drugs, prescribing support tools were rarely used for monitoring. The GPs were generally resistant to cost-cutting measures unless the

effectiveness of treatment could be maintained. The GPs had adopted cost-minimising measures such a generic prescribing, therapeutic equivalent lower cost substitutes and reducing unnecessary prescribing (e.g. antibiotics without clinical indication). GPs were willing to prescribe low cost drugs which were potentially effective before prescribing expensive drugs. This was especially the case for clinical conditions where well-tested drugs were already available. Prosser et al. (Prosser & Walley, 2005) found that cost-effective prescribing was complicated by evidence on cost-effectiveness of treatments, changing drug prices and prescribing of other healthcare professionals (e.g. treatment initiated by other prescriber or hospital consultants).

Bradley conducted a study which explored discomfort and irrationality when making prescribing decisions across a wide range of groups and conditions (Bradley, 1992a, 1992b). The study was conducted in general practices in the North of England where 69 doctors and 5 trainee doctors were recruited for semi-structured interviews. Doctors mentioned new drugs (17.1%) and unfamiliarity with drugs (11.4%) to cause uncertainty about whether they should prescribe a drug or not. Approximately 4% of the doctors cited diabetes drugs as a source of uncertainty (Bradley, 1992a). Drug-related factors which led to discomfort in prescribing were most commonly side-effects and cost of drugs. Other concerns included doubts about indication, effectiveness, clinical appropriateness of the drug (Bradley, 1992a, 1992b). Doctor-related factors included perception of their own role (internal rules for prescribing) and fear of failure to live up to their own expectations made it difficult to refuse prescribing. Additionally, lack of time in the consultation and using prescriptions as 'bargaining chip' to end the consultations were also mentioned as cause for uncertainty (Bradley, 1992a). Patient-related factors mentioned by doctors were age (prescribing for children and elderly patient caused discomfort), social class (prescribing for patients with higher level of education was associated with discomfort) and patient attributes (the patients' knowledge about their condition, expectations and behavioural features) which influenced their prescribing choices. Other concerns mentioned by the doctors were perceived behavioural features such as being demanding, unable to cope with and inability to be reasoned with (Bradley, 1992a). This study also found that improving GP knowledge will not result in behaviour change. The study concluded that doctors have major concerns about preserving the doctor-patient relationship and in order to make changes in their prescribing behaviours these non-clinical factors must be addressed (Bradley, 1992a).

Weiss et al. conducted a study which investigated whether a variety of pressures highlighted by the recent developments in primary care are actually felt as concerns by GPs, and how this influenced their prescribing (Weiss, Fitzpatrick, Scott, & Goldacre, 1996). Twenty-three GPs participated in the interviews and 228 GPs responded to the survey. About 70% of the respondents agreed or strongly agreed that over the years an increasing number of patients were demanding the consultation. This was especially a challenge in antibiotic prescribing. A high number of patients (80%) had unrealistic expectations to what the doctor could do to help them. Around 70% of doctors found it easier to make prescribing decisions for well-informed patients. More than 50% of the respondents found that the only way to finish a consultation was to write a prescription. Forty five percent agreed or strongly agreed and 21.5% were neutral to the statement that emphasis on value for money has helped them improve their

prescribing. About 60% of the doctors believed that patients have the right to unbiased medical advice uninfluenced by cost considerations. The study concluded that there is continued need to monitor how fundholding and hospital prescribing practices influence primary care doctors prescribing behaviours.

1.3 Implementation of prescribing guidance in clinical practice

Sheldon et al. conducted a study which assessed the pattern of implementation of NICE guidance by healthcare organisations (Sheldon et al., 2004). The study reviewed case notes, surveyed and interviewed participants from acute and primary care trusts in England and Wales. The uptake of NICE guidance was variable depending on the topic and level of trust in the guidance. The study found that the likelihood of implementation of a prescribing guideline was higher if it was clear, based on understanding of clinical practice, strong evidence base and was supported and disseminated by professional bodies.

Wathen et al. explored the attitudes to NICE guidance and investigated changes in prescribing patterns among GPs in North Devon Primary Care Trust (Wathen & Dean, 2004). Five selected technology appraisals which were considered most likely to impact GP' prescribing were surveyed. The study found that NICE guidance on its own had little impact on the GPs' prescribing behaviours. GPs received advice and information from local and international sources. When technology appraisals coincided with information from other sources or personal experience there was an increase in prescribing; however, this increase was not sustained over time.

The views on the implementation of clinical guidelines were explored by Rashidian and Russell (2007) in a study including 13 academic and 12 non-academic GPs in Britain (Rashidian, Eccles, & Russell, 2007). The GPs described the barriers to implementation of guidelines such as lack of trust in the content of the clinical guideline (due to quality of evidence that had been used to produce the guideline), lack of trust in the source of clinical guidelines (independent information sources were more favoured), complexity in presentation of guideline (e.g. guidelines are often lengthy and lack a clear treatment algorithms), pressure from influential people (e.g. patients, colleagues within the practice, local consultants), lack of effective implementation strategies (e.g. unavailability of tests and diagnostic tools, reiteration of key changes in guidelines, use of audits to of GPs prescribing to encourage change). Lastly, the authors reported that GPs found a revision of guidelines to be frustrating and this could hinder implementation of the guidelines.

Owen-Smith et al. conducted in-depth interviews (n=52) with professionals involved in healthcare provision at the community level, and with clinical professionals and patients providing or receiving care for morbid obesity and breast cancer (Owen-Smith, Coast, & Donovan, 2010). The study found that NICE guidance was well-regarded among the interviewees however the guidance was more useful to the healthcare manager than clinical professionals. The clinicians implemented the guidance depending on whether the recommendations accorded with their own personal interpretation of available evidence. Further, many of the patients had not heard about the guidance in question, and those who had were not able to use their knowledge to negotiate when treatment was refused.

1.4 Current state of type 2 management in primary care

1.4.1 Time trends, glycaemic responses and cost of antidiabetic medicines

Curtis et al. (Curtis et al., 2018) investigated the variation in second-line prescribing patterns and prescribing costs of antidiabetic treatment in England between 1998 and 2016. They used prescription data from the Clinical Practice Research Datalink (CPRD), a UK-representative database of anonymised primary care electronic health records and annual Prescription Cost Analysis (PCA) data to calculate the prescribing rates per class. The authors found that metformin was used consistently as first-line treatment in accordance with prescribing guidelines (second-line use decreased from 60% to 5%). In the same time period the use of sulfonylurea as first-line treatment decreased from approximately 62% to 5%. There was an extensive geographical variation in the choice of second- and third-line treatment therapies. DDP-4i were the most commonly used second-line treatment in 2016 (43%) followed by sulfonylurea (34%). The use of SGLT2i as second-line and third-line were 14% and 27%, respectively. The prescribing data by Clinical Commissioning Groups (CCGs) showed that there was a noticeable national variation in the prescribing volume of all available therapies except from metformin which has a relatively low variation (55.6%±2.9%). Further, the average spending per patient ranged from £60 to £200 across CCGs. High cost per patient was attributed to increased prescribing rates of high-cost drug classes such as DDP-4i and SGLT-2i. The study found that lack of good evidence to guide antidiabetic medicines prescribing after metformin had led to extensive variations in drug choices across regions.

Heald et al. (Heald et al., 2018) conducted a study using publicly available data and results from National Diabetes Audit 2013/2014 and 2014/2015 to determine how a variety of pre-defined factors could influence glycaemic outcome on practice level, and how the clinicians' prescribing choices may influence the proportion of patients achieving glycaemic control. The increase in volume and cost of antidiabetic drugs was attributed to the launch and use of DDP-4i, GLP-1RA and SGLT2i. The study found that the use of new therapies accounted for 41% of the medicines budget only divided over 9% of the total number of patients. Moreover, significant differences in HbA1c outcomes (median=67.3%) were observed across the surveyed practices. In those general practices where the NICE benchmark of HbA1c 58mmol/mol (≤7.5%) was successfully achieved, the 90th percentile was 75.4% and 10th percentile was 57.7% of patients. The study found that general practices which had better treatment outcomes had a higher proportion of elderly patients on their patient list, provided more effective diabetes services (including case identification, care checks, patient education, percentage of patients with blood pressure and cholesterol under control and more patients with type 1 diabetes achieving target HbA1c levels) and overall had a lower prescribing expenditure per patient. Additionally, these general practices prescribed less sulfonylurea, insulin, GLP-1RA and more metformin, DDP-4i and blood glucose monitoring strips for patients with T2D. Further, general practices with higher expected prevalence of T2D in the local population had poorer glycaemic control. General practice with a majority of socially disadvantaged patients were associated with poorer management of higher-risk patients (HbA1c of >10%). The study did not find any relationship between glycaemic control and ethnicity nor social deprivation. The study concluded that the overall healthcare costs of managing diabetes-related complications could be reduced if all practices brought their service and medicines to the level of the

90th percentile. This would mean additionally 213,000 patients would achieve total glycaemic control, and higher-risk patients would be reduced with 62,000 patients. (Heald et al., 2018).

A study which collected primary care data in the period between 2010 and 2017 looked at time trends in prescribing of antidiabetic medicines in the UK (Dennis et al., 2019). This study showed that the use of DDP-4i increased from 22% to 41% during the study period. This means that DDP-4i have replaced sulfonylurea (53% versus 29%) as the most common second-line treatment. The total prescribing of SGLT-2i as first to fourth line was 17% in 2017 (introduced in 2013). Treatment discontinuation after initiation of first-line therapy when treated with any drug remained constant over time (4% versus 3%). The study concluded that changes in prescribing of antidiabetic medicines had not resulted in a change in glycaemic responses among patients and had only led to modest improvement in other clinical outcomes.

1.4.2 Treatment intensification and dose distribution

A UK based study collected administrative data from more than 80,000 people in the period 2006 to 2011 (Khunti, Wolden, Thorsted, Andersen, & Davies, 2013). The study sought to investigate the time to treatment intensification for patients on between one and three oral antidiabetic medicines. It was found that the median time before starting second-line treatment was 2.9 years. Further, the study found that the mean HbA1c level at which the intensification of treatment happened was 8.7%, 9.1% and 9.7% for one, two or three oral antidiabetic medicines. The study concluded that there were delays in intensification of treatment among patients with T2D despite inadequate glycaemic responses to treatment.

Paul et al. (Paul, Klein, Thorsted, Wolden, & Khunti, 2015) investigated the effect of delay in treatment intensification on the risk of macrovascular events. The study used retrospective UK patient register data from >100,000 people collected in the period 1990 to 2012. The mean HbA1c at diagnosis was 8.5% (65 mmol/mol). It was reported that at two years after diagnosis patient with steady HbA1c levels above 7.0% (53 mmol/mol) and 7.5% (58 mmol/mol) had never received any treatment intensification in 26% and 22% of cases, respectively. The study found that in patients with HbA1c above 7.5%, a one year delay in treatment intensification caused significant increased risk of myocardial infarct (67%), stroke (51%) and composite macrovascular events (64%). Overall, the study concluded that delays in treatment intensification increased the risk of myocardial infarct, stroke and composite macrovascular events.

Desai and colleagues investigated the time to treatment intensification after monotherapy and the association between the timing of treatment intensification and subsequent glycaemic control among patient with T2D (Desai et al., 2018). The study used patient data from >93,000 patients and was collected between 2000 and 2014 for patient who achieved HbA1c levels above 7.0% (53 mmol/mol). The study found that the median time from intensification to control were 20.0, 24.1 and 25.7 months, respectively for early, intermediate and late treatment intensification cohorts. The likelihood of attaining glycaemic control was 22% and 28% lower for the cohorts from the groups intensified intermediate or

late on treatment as compared to those who intensified early. The study concluded that earlier treatment intensification was related to shorter time to glycaemic control regardless of if metformin or sulfonylurea had been used as first-line treatment.

The study conducted by Iglay et al. (Iglay et al., 2020) assessed the dose distribution and up-titration among patients on metformin monotherapy. The studied assessed dose distribution among new users of metformin and existing users of metformin at 6 months and 12 months. It was found that 72% and 54% of new users and existing user, respectively received doses between >0 mg and ≤1000 mg. Among new users 6.7% and 10.8% had been up-titrated at 6 months and 12 months. The study concluded that dosing of metformin was suboptimal and up-titration in the first year of treatment was infrequent among patients treated with metformin first-line treatment.

1.4.3 Adherence to prescribed antidiabetic medicines

Farmer at al. used two retrospective databases in the UK to investigate the prevalence of nonadherence to treatment for patients with T2D and potential associations between type of antidiabetic medicines and HbA1c reduction (Farmer et al., 2016). Patients who were newly diagnosed and had received metformin, sulfonylurea, thiazolidinediones pr DDP-4i continuously for at least one year were eligible for this study. Good adherence to prescribed treatment was defined as a medication possession ratio ≥0.8. Overall, adherence to prescribed antidiabetic medicines varied across treatments. Highest percentage of nonadherence was to metformin treatment (18.8%). Lowest nonadherence was to thiazolidinediones (8.6%) followed by DDP-4i (9.1%). The nonadherent group had a lower (0.38%) reduction in HbA1c as compared to the adherent group (0.75%). The study concluded that nonadherence to common antidiabetic medicines is associated with smaller reduction in HbA1c levels. Further, it suggested that the lack of response to treatment could be due to inconsistent use of treatment.

A UK based study evaluated changes in HbA1c, weight and treatment persistence among patients with T2D in the period 2013 and 2014(Wilding et al., 2018b). The three parameters were assessed every 6 months until 18 months. The study found that the lowest incidence of changes in therapy was found among patients on combination of metformin and SGLT-2i (42.3%) closely followed by metformin and DDP-4i (46.8%) at 18 months. There was a reduction in HbA1c among patients on all treatments. Further, those patients treated with combination of metformin and SGLT-2i or DDP-4i achieved the highest reductions in HbA1c. Patients treated with metformin and SGLT-2 were also more likely to achieve composite endpoints of HbA1c reduction of more than 0.5%, lose more than 2kg and continued treatment until 18 months.

A retrospective study examined adherence to antidiabetic medicines among patients offered organised diabetes care from a large general practice in Newmarket, England (White et al., 2011). Data was collected over a two month period for 60 patients who were on oral antidiabetic medicines It was reported that only four patients took less than 90% of prescribed doses of antidiabetic medicines. Patients treated with more than once daily doses were less adherent than those on once daily treatment

regimens. The study also found that patients adhered less to metformin than other treatments. It was concluded that low adherence among patients with worsening HbA1c levels should be considered before moving onto treatment intensification or treatment switch. This was especially recommended for those patients whose prescribed treatment was dosed more than once daily. However, it was emphasised that the level of adherence may be overestimated due to selective sampling of patients and use of Medicine Event Monitoring System.

1.5 Clinical management of patients with type 2 diabetes in England

In this section, studies on current management and challenges in effective management of T2D in primary care setting are presented.

1.5.1 Type 2 diabetes in adults: management (NG28)

NG28 is the most commonly used prescribing guideline for T2D in England and Wales. NICE defines the goal of T2D treatment as "*aimed at minimising the risk of long-term microvascular and macrovascular complications by effective blood-glucose control and maintenance of HbA1c at or below the target value set for each individual patient" (NICE, n.d.-c).*

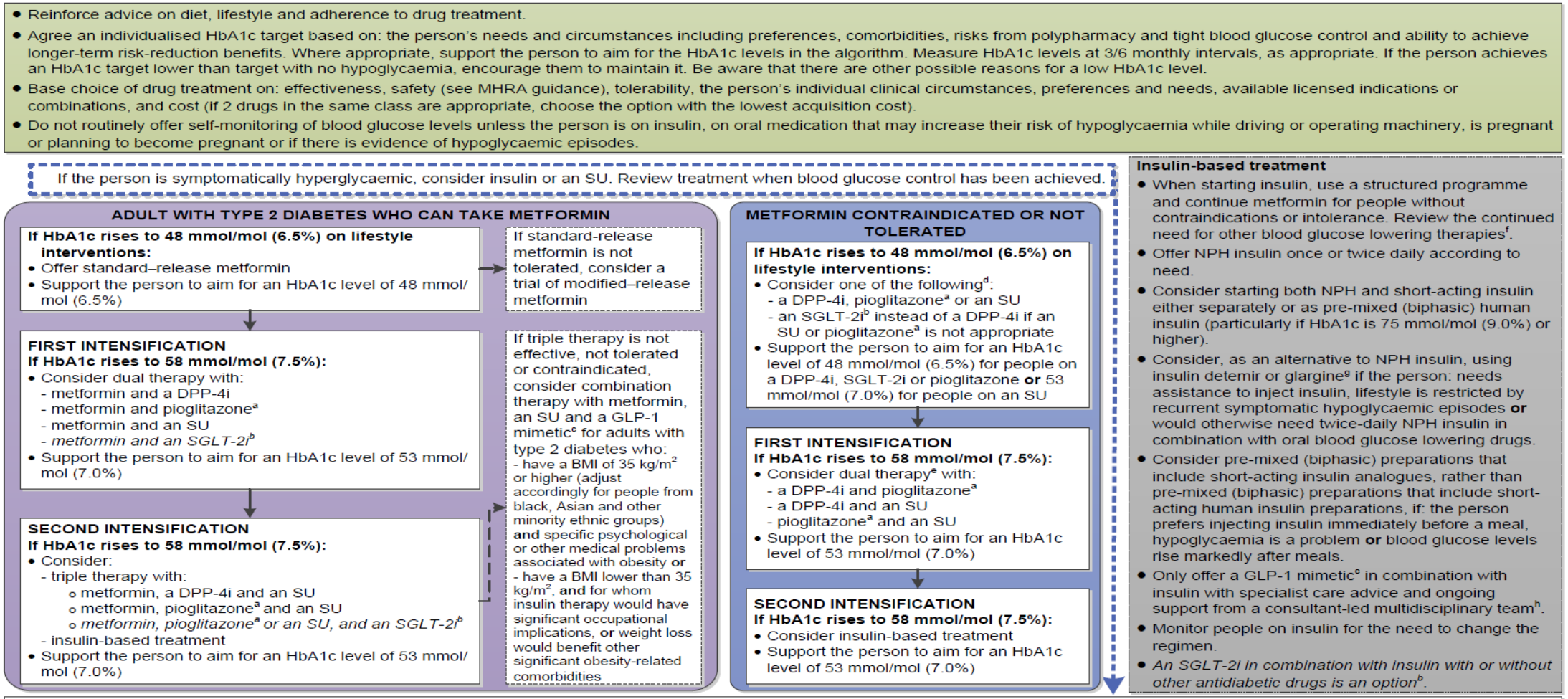
The first NICE guidance on T2D was published in 2002 (NICE, 2002) followed by another guidance in May 2008 (NICE, 2008), and the subsequent glycaemic update in May 2009 (NICE, 2009). The latest guidance on T2D from NICE was published in December 2015 (referred to as NG28 hereon), and has last been updated in 2017(NICE, 2015). NG28 has five focus areas:

- Patient education.
- Dietary advice.
- Managing cardiovascular risk.
- Managing blood glucose levels.
- Identifying and managing long-term complications.

Non-pharmacological treatment includes reinforcing advice on diet and lifestyle however there is no specific diet that which has been endorsed. The importance of considering blood pressure management, antiplatelet therapy and lipid management is also emphasised. Additionally, clinicians are made aware when drug treatment recommendations are outside the licensed indication.

Figure 1.3 is adapted from NG28 (NICE, 2015) and provides key guidance on therapeutic management of adults following diagnosis of T2D. Below are key summary points from NG28:

- Since the last guidance was published in 2009 a number of new antidiabetic medicines have become available and most of these have been considered in the new guidance. The recommendations on the use of insulin have changed very little.



Abbreviations: [DPP-4i]Dipeptidyl peptidase-4 inhibitor, [GLP-1]Glucagon-like peptide-1, [SGLT-2i]Sodium–glucose cotransporter 2 inhibitors, [SU]Sulfonylurea. Recommendations that cover DPP-4 inhibitors, GLP 1 mimetics and sulfonylureas refer to these groups of drugs at a class level.

a. When prescribing pioglitazone, exercise particular caution if the person is at high risk of the adverse effects of the drug. Pioglitazone is associated with an increased risk of heart failure, bladder cancer and bone fracture. Known risk factors for these conditions, including increased age, should be carefully evaluated before treatment: see the manufacturers' summaries of product characteristics for details. Medicines and Healthcare products Regulatory Agency (MHRA) guidance (2011) advises that 'prescribers should review the safety and efficacy of pioglitazone in individuals after 3–6 months of treatment to ensure that only patients who are deriving benefit continue to be treated'.

b. See NICE technology appraisal guidance 288 & 418, 315 and 336 on dapagliflozin, canagliflozin and empagliflozin, respectively. All three SGLT-2 inhibitors are recommended as options in dual therapy regimens with metformin under certain conditions, as options in triple therapy regimens and in combination with insulin. All three are also options as monotherapies in adults in whom metformin is contraindicated or not tolerated. Serious and life-threatening cases of diabetic ketoacidosis have been reported in people taking SGLT-2 inhibitors (canagliflozin, dapagliflozin or empagliflozin) or shortly after stopping the SGLT-2 inhibitor. MHRA guidance (2015) advises testing for raised ketones in people with symptoms of diabetic ketoacidosis, even if plasma glucose levels are near normal.

c. Only continue GLP-1 mimetic therapy if the person has a beneficial metabolic response (a reduction of HbA1c by at least 11 mmol/mol [1.0%] **and** a weight loss of at least 3% of initial body weight in 6 months).

d. Be aware that, if metformin is contraindicated or not tolerated, repaglinide is both clinically effective and cost effective in adults with type 2 diabetes. However, discuss with any person for whom repaglinide is being considered, that there is no licensed non-metformin-based combination containing repaglinide that can be offered at first intensification.

e. Be aware that the drugs in dual therapy should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug.

f. MHRA guidance (2011) notes that cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for the development of cardiac failure. It advises that if the combination is used, people should be observed for signs and symptoms of heart failure, weight gain, and oedema. Pioglitazone should be discontinued if any deterioration in cardiac status occurs.

g. The recommendations in this guideline also apply to any current and future biosimilar product(s) of insulin glargine that have an appropriate Marketing Authorisation that allows the use of the biosimilar(s) in the same indication.

h. A consultant-led multidisciplinary team may include a wide range of staff based in primary, secondary and community care.

Figure 1.3 National Institute for Health and Care excellence's (2015) therapeutic algorithm for type 2 diabetes.

- The GDG recommends that the choice of treatment should be based on effectiveness, safety, tolerability, individual circumstances (for example co-morbidities), polypharmacy, patient preference, licensed indications and acquisition cost.
- The patient is given autonomy and the physician is advised to choose an appropriate choice for treatment after fully informing and discussing the benefits and side-effects of the proposed treatment.

In the NG28 it is recommended to start patients on diet and lifestyle interventions, and reinforce this advice at every step of treatment (NICE, 2015). If HbA1c rises above 48mmol/mol (6.5%) it is recommended to initiate pharmacological treatment. Metformin is recommended as first-line treatment, and it is recommended to optimise the dose over a few weeks to maintain HbA1c levels at or below 48mmol/mol (6.5%) or 53mmol/mol (7.0%). If these criteria are not met with metformin treatment, it is recommended to either intensify treatment by adding another treatment or switching to another drug (*see treatment algorithm presented as figure 1.3*). Currently the most commonly used drug classes used to treat T2D in England includes biguanides, sulfonylurea, thiazolidinediones, DDP-4i, insulin, GLP-1RA and SGLT-2i. Other less frequently used drug classes include meglitinides and acarbose. As the focus of the current thesis is on antidiabetic drug classes for the treatment of T2D, the recommendations on bariatric surgery, blood pressure management, antiplatelet therapy and managing complications have not been elaborated. Further, prescribing recommendations for children, pregnant, breastfeeding women and the elderly are also excluded.

1.5.2 Concerns and critique of NICE prescribing recommendations

Since it was announced that CG87 (NICE, 2009) was due to for an update groups of diabetes practitioners from primary and secondary care came together and wrote commentaries which discussed the shortcomings of the guidance proposed by NICE. The criticism and concerns targeted recommendations on the choice of drugs, the sequence of drugs and glycaemic target levels as well as the usefulness of the recommendations in clinical practice. The authors of the commentaries were diabetes practitioners and were voicing their concerns hoping that NICE would listen and make changes to the produced draft guideline. The first draft proposal was published in January 2015 (NICE, 2015). Much of the criticism of the first draft proposals was regarding the following recommended treatment therapies:

- Repaglinide recommended as first-line for those who cannot tolerate metformin and as possible second-line treatment.
- Pioglitazone was recommended as principal second-line agent to metformin.
- The guidance suggested that routine glucose monitoring of patients with T2D was not necessary.
- GLP-1RA were only recommended for patients with Body Mass Index (BMI) >35 km/m^2.

- T2D patients who were prescribed insulin were not offered treatment on equal basis with Type 1 diabetes mellitus patients.
- No recommendation for use of SGLT2i.

Following a second consultation, a revised draft proposal was published in June 2015 (NICE, 2015). Again, a number of commentaries were published regarding the recommended treatment therapies:

- Revised draft proposal was described as a 'waiting for failure' approach to management.
- Concerns that repaglinide was still in the treatment algorithm and recommended as second-line treatment.
- Concerns about the risk of hypoglycaemia when using sulfonylurea.
- Concerns about continued recommendation of pioglitazone as principal second-line agents to metformin.
- Concerns about that DDP4i were presented *after* pioglitazone and repaglinide in the treatment algorithm.
- DDP4i were given equal preference to sulfonylurea.
- Concerns about GLP-1RA stop rules and BMI restrictions.
- Continued concerns about recommended use of insulin
- Very little mention and positioning of SGLT-2i in treatment regimen

Adaption of NICE guidance in clinical practice

Overall, Chaplin (2016) found that there had not been a great change between previous NICE guidance on T2D and NG28 (Chaplin, 2016). Other authors stated that the revised draft proposal was lengthy (342 pages) and hence it would not be possible for generalist front-line clinicians to read the guidance (Hillson, 2016; O'Hare et al., 2015a; O'Hare et al., 2015b). Further, there was a request for a simple and clear treatment algorithm to aid the use of the guidance in practice. The final NG28 included a treatment algorithm, however it was found that this had many references and footnotes (Hillson, 2016) which were complex, confusing and lacked simplicity (O'Hare et al., 2015) as compared to the updated position statement produced by ADA-EADS (Inzucchi et al., 2015).

O'Hare et al. (O'Hare et al., 2015) disagreed on the choice of drug treatments recommended in the draft guideline (NICE, 2015) and found that if the guidance became part of the final guideline the recommendations would either be ignored or the clinicians would be forced to 'pay lip service'. In either case the authors found that NICE failed to provide clear, credible and cost-effective recommendations for prescribing. Further, the draft guideline and revised draft guideline (NICE, 2015) did not consider evidence on SGLT-2i, and nor was it given an important position in treatment regimen. For this reason it found that the final guideline was at risk of not being up-to-date with current evidence at the time of publication (O'Hare et al., 2015). It was also noted that NG28 referred to individual drug classes instead of medicines (Hillson, 2016). Finally, Chaplin (2016) pointed out that the problem with guidance lies in the implementation of recommendations in clinical practice (Chaplin, 2016).

Credibility of NICE

The guideline as well as the production of guidelines and NICE's reputation was subject to critique from the diabetes clinicians. O'Hare 2015 warned: "*In our opinion, the draft proposals are so out of kilter with current recommendations for "best practice" that, if enacted, they will reduce quality of care and patient safety and will set back modern diabetes management by decades*." (O'Hare et al., 2015). Hawkes et al. reported the NICE guidance on management of adults with T2D as "*a recipe for failure*" at a seminar in Westminster Health Forum (Hawkes, 2015). Further O'Hare 2015 felt so strongly about the re-evaluation of the recommendations that the authors suggested NICE to adopt and recommend the ADA-EADS consensus report on management of patients with T2D to clinicians (O'Hare et al., 2015). Hillson (2015) defined T2D as condition in search of a definition. The author further elaborated that until we have refined the classification of T2D it is impossible to say what NICE could have done better while developing the T2D prescribing guideline (Hillson, 2016).

Production of guideline recommendations

Diabetes practitioners found that there were paradoxes in the guidelines produced by the GDG. On one hand the recommendations advised that the risk of hypoglycaemia associated with repaglinide was not an issue and the risk of hypoglycaemia associated with insulin use was not a concern and yet the clinicians were asked to consider the risk of hypoglycaemia when choosing between antidiabetic treatments (O'Hare et al., 2015) .

The guideline development group was found not have had enough emphasis on safety and the overall health of the patients and instead weighed between making efficacious and cost based recommendations (O'Hare et al., 2015). It is underlined that there were several differences between the draft proposal and international guidelines (e.g. ADA- EADS consensus report) as well as common practice in the UK and the rest of the globe (O'Hare et al., 2015). The GDG was for instance asked to address evidence behind the recommendations for repaglinide and pioglitazone being used as second- and third-line treatments. One group of authors (O'Hare et al., 2015) suggested that repaglinide should be removed from the recommendations for several reasons; Firstly they highlighted that the GDG missed that fact that repaglinide was not licensed to be used as a combination therapy. Secondly, they found that experiences with prescribing repaglinide was short term (12 months) and there was no evidence on the sustained effect with more prolonged therapy. Thirdly, it was recommended that DDP-4i should be given prominence as second-line treatment and downgrading pioglitazone (O'Hare et al., 2015). It was pointed out that DDP-4i and thiazolidinediones have different side-effect profiles. According to the authors DDP-4i are commonly used in the UK as second-line to metformin in overweight and obese patients when HbA1c >53 mmol/mol (>7.0%) and that there was established evidence (Green et al., 2015) for the long-term safety of DDP-4i (weight neutral, do no cause hypoglycaemia and does not require close monitoring of patient).

Gaps in the use of scientific evidence

There were concerns that the first consultation for the update of the CG89 in 2015 concluded before the latest clinical trial evidence on drugs with cardiovascular benefits could be appraised (Hillson, 2016; O'Hare et al., 2015). Clinical trial outcomes on SGLT-2i, DPP-4i and lixisenatide were among others mentioned to be precluded from the guidance (Fisher, 2015; Hillson, 2016). The preclusion of drugs used in clinical practice was especially a concern to the diabetes practitioners as they were aware that NICE prescribing guidelines are not likely to be updated frequently (Fisher, 2015; O'Hare et al., 2015).

Glucose management

The draft proposal recommended to wait until HbA1c rises to above 58 mmol/mol (7.5%) before intensifying treatment. This is described as being the 'waiting for failure' approach by O'Hare and colleagues (O'Hare et al., 2015). Following the revised draft proposal O'Hare et al. recommend the GDG to provide better guidance on HbA1c thresholds for treatment intensification (O'Hare et al., 2015). Similar to O'Hare and colleagues, Meetoo et al. found that this approach was unlikely to promote overall glycaemic control (Meetoo & Alsomali, 2016). Further, they questioned why it has been recommended to lower the blood glucose targets to 53 mmol/mol, 7.0% when drugs that can produce hypoglycaemia are introduced. They argue that a number of therapies are available which does not impose the risk of hypoglycaemia and hence only a very little number of patients should need treatment which induces hypoglycaemia e.g. sulfonylurea (Meetoo & Alsomali, 2016).

The recommendation of relaxing the HbA1c target in the elderly was welcomed by diabetes practitioners (Meetoo & Alsomali, 2016). This recommendation was supported by clinical trial data which emphasise on the importance of early glycaemic control and the benefits of reducing macro- and microvascular disease (Holman, Paul, Bethel, Matthews, & Neil, 2008). This concurs with findings from international clinical trials such as The Action to Control Cardiovascular Risk in Diabetes (ACCORD) (Gerstein et al., 2008), VADT (Duckworth et al., 2009) and The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) (Patel et al., 2008).

Glucose monitoring

The guidance on self-monitoring of blood glucose is welcomed by diabetes practitioners. The NG28 advises that routine glucose monitoring of patients with T2D is not necessary. Further, it is recommended that this should only be offered to patients at risk of hypoglycaemia. The diabetes practitioners appreciate that the recommendation is due to the increasing cost related to glucose monitoring and lack of well-designed clinical trials to measure the effectiveness of the use (Farmer et al., 2007). However, the diabetes practitioners found that there is economic sense in following this recommendation for average CCGs which spends £1.5m on glucose monitoring and £3.5m on drugs (O'Hare et al., 2015). However some patients are psychologically dependent on glucose monitoring and there must be taken appropriate consideration of their needs (O'Hare et al., 2015).

Individualised care

An individualised approach to diabetes care is welcomed as it allows the clinicians to use their clinical judgement and hence not be pressurised to use less-optimal treatments for their patients (Hillson, 2016; O'Hare et al., 2015). The draft proposal recommend customising and tailoring treatment to the individuals' needs and safety. This recommendation was well-liked among the diabetes practitioners (O'Hare et al., 2015). However, the same consideration for the individual is not given when choosing appropriate drug therapy (O'Hare et al., 2015). Nevertheless, the diabetes practitioners emphasized that this would require the clinicians to have knowledge about the available treatments and sufficient consultation time with the patients. Further the choice of drug would also depend on the patients' abilities to participate in the shared decision-making (O'Hare et al., 2015). Hillson (2016) asked clarifying questions: "*But which treatment really is best for which patient? And if targets are used, what does success look like? It cannot be 100% achievement if treatment is individually tailored*." (Hillson, 2016).

Diet and lifestyle

Diet and lifestyle interventions are recommended as initial management in NG28. Although O'Hare et al. found that there is little evidence to support this recommendation they were supportive of the recommendation (O'Hare et al., 2015). According to the National Diabetes Audit (NDA) (2014/15) 78% of patients diagnosed with T2D were offered structured education but only 5.3% of the patients attended (Health and Social Care Information Centre, 2016). The conclusion from the NDA was that "*The focus of all should be on how to increase the number of people who attend structured education*," (Health and Social Care Information Centre, 2016). However, the NICE guidance did not provide any further guidance on how to increase attendance (Chaplin, 2016). The guidance emphasizes that there are no long-term trials of efficacy of low-carbohydrate diet. Further, there is no recommendation towards changing current practice for diet and lifestyle recommendations in clinical practice.

1.6 Rationale of the PhD thesis

It is well-established in the literature that the prevalence of T2D in England is increasing (NHS Digital, 2020b). Clinical trials also show that many of the newly launched treatments seem to have good prospects for treating patients with T2D. However statistics from NDA over the years have shown that patients have suboptimal outcomes from their treatment (Health and Social Care Information Centre, 2016; NHS Digital, 2018). Nevertheless, the complex sequencing and combinations of treatments therapies has made it difficult to evaluate the benefit of the current treatment approaches in clinical practice. Retrospective database studies have shown that patients have higher HbA1c levels than indicated by NICE when they start their first pharmacological treatment. Further, the patients are not prescribed maximum dose of metformin before the treatment is switched or intensified. Studies have also found that nonadherence to treatment at all stages of therapy is common and is associated with reduced clinical outcomes. Lack of adequate glycaemic control is associated with increased risk of

micro- and macrovascular complications (Paul et al., 2015). Additionally, onset and progression of diabetes-related complications can be delayed by improving glycaemic control (Bailey, Del Prato, Eddy, Zinman, & Global Partnership for Effective Diabetes, 2005). Yet, the literature demonstrates that there are delays in intensification of treatment in patients with T2D at all stages of treatment (Desai et al., 2018; Iglay et al., 2020). Research about general practitioners' antidiabetic medicines prescribing practices, and what influences their day-to-day prescribing in primary care remains limited. Hence this mixed-methods study has been planned in this context.

1.7 Overview of aims and objectives

After carefully reviewing the existing literature, two main research gaps were identified. Firstly, there was a lack of clear evidence to support the role of NICE guidance in clinical practice when managing adults with T2D. Secondly, there is need for further evidence to support primary care healthcare professionals in navigating the growing number of treatments for T2D. As mentioned earlier, there is anecdotal evidence that the current NG28 prescribing guidelines do not support primary care healthcare professionals sufficiently. It is the aim of this study to gather evidence on primary clinicians' prescribing practices, and conduct research which could inform future policy and practice to overcome the identified limitations of current evidence.

First, it was sought to understand the current antidiabetic prescribing patterns and the cost of antidiabetic medicines in a global context, and hence two systematic literature reviewswere conducted. The objectives were:

1. Which antidiabetic drug classes are being prescribed in primary care?
2. Which antidiabetic drug classes are used during treatment initiation?
3. What is the cost of prescribed antidiabetic medicines?

The methodology, findings and discussion of the findings from the two systematic literature reviews are described and discussed in chapter 2.

The second aim was to investigate how clinicians prescribe antidiabetic medicines in primary care in order to narrow the gap between clinical practice and prescribing guidelines. The objectives were:

1. Which antidiabetic medicines are prescribed during the management of adults with type 2 diabetes in primary care?
2. What influences GPs' antidiabetic medicines prescribing decisions in primary care?
3. What are the challenges in using antidiabetic medicines in primary care?

An exploratory mixed-methods research design was used to provide a comprehensive understanding of what drives the healthcare professionals' prescribing choices. In the qualitative stage (study 1) semi-structured interviews were conducted with GPs. This was followed by a quantitative stage (study 2) where antidiabetic medicines prescribing practices of GPs, nurses and practice pharmacists were surveyed. The mixed methods study was followed by a case study (study 3) which aimed to compare

the treatment price of two GLP-1RA treatments in a cross-national study. Specific research questions for each study have been described in the respective chapters of the PhD thesis.

1.8 The structure of the thesis

This research was informed by a general review of existing literature and two systematic literature review informed the planning and conduct of the mixed-methods study. The outline of the thesis has been depicted in figure 1.4, and each chapter has been described below.

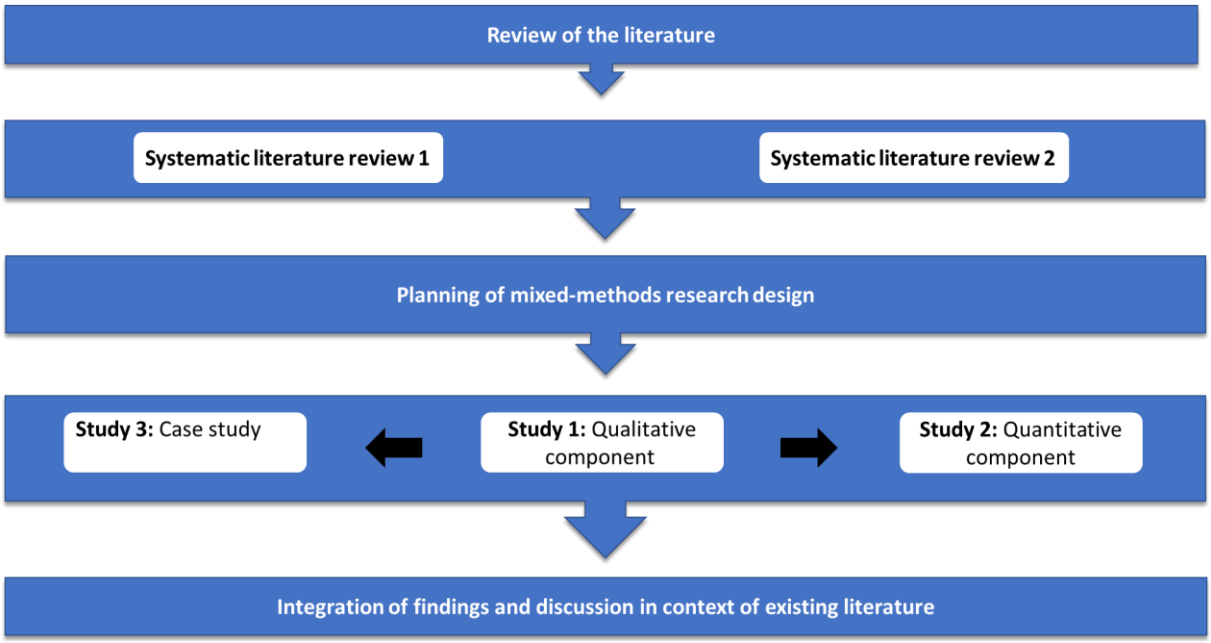


Figure 1.4 Outline of thesis chapters

Forewords provided contextual background of this PhD research. The author of this PhD thesis introduced the reader to her PhD journey, motivation for conducting this PhD research and the research team.

Chapter 1 presented a review of the literature which gives the reader a broader picture of why it is important to investigate primary care clinicians' antidiabetic medicines prescribing practices. This was followed by a presentation of the rationale of the study, an account of author's reflections in regard to gaps in the literature and finally the overall aim of this PhD research.

Chapter 2 describes the methodological process of conducting a systematic literature review (part I) followed by a systematic literature review on antidiabetic medicines prescribing trends in primary care (part II) and cost of antidiabetic medicines (part III), respectively. Finally, the key literature from chapter 1 and chapter 2 which informed the conduct of this research is summarised.

Chapter 3 describes the mixed-methods research designs, researchers' philosophical stance and conceptual framework used in this thesis. This is followed by a justification of why exploratory mixed-methods research is appropriate to answer the posed research questions. In this chapter a detailed

encounter of the choice of method and sampling framework and recruitment process are also discussed. To ensure clarity in the research process the methods used in study 1 and 2 are described and justified in turn.

Chapter 4 presents aims and objectives of the qualitative study (study 1) followed by a description of the results. This commences with an overview of the overarching themes followed by a presentation of GPs' beliefs and behaviours which are supported by anonymised quotations. A conceptual model was developed to describe key influences on GPs prescribing practices in primary care.

Chapter 5 presents the aims and objectives of the cross-sectional study (study 2). Then, the findings are presented. The findings are facilitated by tables and figures which summarises the findings.

Chapter 6 presents aims and objectives, applied methods and results of a cross-national case study which compares the prices of two antidiabetic medicines (study 3). The findings are illustrated by tables and figures which facilitates the comparison of treatment prices across the surveyed countries.

Chapter 7 takes the findings from the three sub-studies to an analytical level by starting to draw comparison between the studies. Then the research is discussed in context of existing literature. Lastly, strengths and limitations of the research design has been discussed.

Chapter 8 concludes on the findings of this PhD thesis and makes recommendations for future research and policy and practice.

Finally, it is important to make a distinction between the terms and terminologies used in this PhD thesis. When referring to the overall PhD thesis, 'mixed-methods study', and 'research' is used. Study 1 is also referred to as 'qualitative interviews' and 'qualitative study'. Study 2 is also referred to as 'survey' and 'quantitative study'. Lastly, study 3 is also referred to as 'pricing study' and 'case study'. The author of this PhD thesis is also referred to as 'researcher'.

CHAPTER 2

Systematic Literature Reviews

2.1 Introduction

In the first chapter, selected literature on General Practitioner' (GPs) use of prescribing guidelines, influences on GPs' prescribing behaviours and current management of adults with type 2 diabetes (T2D) in primary care in England was described. This current chapter aims to gather evidence on antidiabetic medicines prescribing trends and cost antidiabetic medicines in a structured manner and critically appraise the current state of knowledge on the subject both inside and outside England. The majority of the literature on prescribing trends and cost of antidiabetic medicines reported on these trends separately, hence two systematic literature reviewa have been conducted.

This chapter has been divided into four parts. Part I titled, "*Introduction to Systematic Literature Reviews*" will provide the rationale and theoretical background for this systematic literature review. Part II of the chapter is titled, "*Trends in global prescribing of antidiabetic medicines in primary care*" will explore antidiabetic medicines prescribing trends in primary care across the globe. This systematic literature review has been registered with The International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42017074974). The findings are published in *Primary Care Diabetes*, and tables and figures have been adapted from this publication (Ramzan, Timmins, Hasan, & Babar, 2019b). Part III of the chapter titled, "Cost of antidiabetic medicines", will provide a global comparison of expenditures on antidiabetic medicines. An unpublished PROSPERO record is available for this systematic literature review. The findings from this systematic literature review have been published in *Expert Review of Pharmacoeconomics & Outcomes Research,* and tables and figures have been adapted from this publication (Ramzan, Timmins, Hasan, & Babar, 2018). The final part is titled," *Key summary points from chapter 1 and 2"*, which presents a reflective summary of the presented literature in chapters 1 and 2, and its implementation in current thesis.

2.2 Part I: Introduction to systematic literature reviews

According to Moher et al., systematic literature reviews are defined as "*a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review*" (Moher, Liberati, Tetzlaff, & Altman, 2009, p. 264). Systematic literature reviews provide a summary of all available literature and aim to answer one or more research questions on a given research topic (Higgins, 2011). Systematic literature reviews are used to gather structured information and also analyse and critique the literature on a specific topic. They are used for various purposes in teaching settings, informing clinical-decision making and guiding healthcare policies and interventions (Kable, Pich, & Maslin-Prothero, 2012). As previously mentioned, there has been an increase in T2D research over the last 20 years. Due to the increasing literature it is also difficult for researchers and clinicians to stay up-to-date with the latest findings. Recently, the availability of high quality systematic literature

reviews have made it possible for researchers, clinicians and policy makers to make informed decisions without having to locate, read and critically appraise relevant literature on their own (Higgins, 2011).

The Cochrane Collaboration (Higgins, 2011) recommends a seven stage process to conduct a systematic literature review. In the first stage, a well- formulated research question is defined. Further, it must be clearly stated which patients or diseases are included in the intervention. According to Merlin, et al., the basis for good evidence lies in a well-designed research question and a thoroughly conducted SRL (Merlin, Weston, & Tooher, 2009). Moher et al., (Moher et al., 2009) has developed a framework called '*Preferred Reporting Items for Systematic reviews and Meta-Analyses'* (PRISMA) on items to include when reporting a systematic literature review or meta-analysis. The 27-item checklist is used to document important decisions made during the review process, such as adding or removing outcomes. Further, adherence to a systematic literature review protocol minimises the risk of bias (Moher et al., 2009). In second stage, data sources such as databases and grey literature used to retrieve evidence-based literature must be identified. A detailed description of search terms and keyword combinations must be documented. A popular definition of grey literature is as follows: "*that which is produced on all levels of governmental, academics, business and industry in print and electronic formats, but which is not controlled by commercial publishers*" (Hopewell, McDonald, Clarke, & Egger, 2007). Examples of grey literature include conference abstracts, research reports, book chapters, unpublished data, dissertations, policy documents and personal correspondence. It is generally found appropriate to include grey literature in a thorough literature review (Hopewell et al., 2007; McAuley, Pham, Tugwell, & Moher, 2000), but the amount of grey literature is enormous and difficult to access. As it is the aim of this systematic literature review to present the most influential scientific literature, grey literature has not been included in the presented systematic literature reviews. The third stage focuses on critical evaluation of eligible studies. To ensure validity, the intervention must have clearly defined inclusion and exclusion criteria which the studies must adhere to. Flexibility around the inclusion and exclusion criteria are considered necessary and essential to conduct a robust systematic literature review (Tranfield, Denyer, & Smart, 2003). Moher et al., supports this view and further adds that working from a review protocol ensures transparency and reproducibility (Moher et al., 2009). Most systematic literature reviews in health services research are registered with PROSPERO (NIHR, n.d.). The fourth stage focuses on data collection. In order to allow for comparison between studies, methodology (relevant variables, sample size and data analysis) and results of each study must be described in great detail. The fifth stage concerns the analysis and reporting of the gathered data. The reviewer must ensure that findings are analysed and grouped according to their methodology. Results should be tabulated and presented so they are easy for the reader to understand. If statistical analysis is applied, this must also be described in detail. There are a number of tools available to appraise qualitative and quantitative literature (Kable et al., 2012). Quality appraisal of the selected papers helps with identifying studies which are poorly designed, inadequately described, biased or limited due to their methodology (Evans, 2004). In the sixth stage, the gathered findings must be interpreted and compared with relevant literature. During this stage it is important to reflect on the methodological limitations of the conducted systematic literature reviews. SYSTEMATIC LITERATURE REVIEW The final stage concerns the dissemination of the findings. In order for researchers, clinicians and policy makers to benefit from the

systematic literature review it must be refined and updated when substantial new evidence becomes available on the topic.

2.3 Part II: Trends in global prescribing of antidiabetic medicines in primary care

In this section antidiabetic medicines prescribing trends in primary care are reviewed.

2.3.1 Aim and objectives

The aim of this systematic literature review was to examine changes in the use of diabetes medicines prescribed to treat T2D in the primary care setting. The specific research questions were:

1) Which antidiabetic drug classes are being prescribed in primary care?
2) How frequently is each antidiabetic drug class being prescribed?
3) Which antidiabetic drug classes are used during treatment initiation?

2.3.2 Methods

This section describes the search strategy, participants, outcomes measure, data extraction and synthesis.

2.3.2.1 Search strategy

Comprehensive database searches were conducted in Pubmed, Medline, Springer Link, Scopus and Science Direct. The searches used keyword combination of “type 2 diabetes”, “diabetes”, “antidiabetic”, “glucose lowering drugs”, “prescription pattern”, “prescription patterns”, “prescription rate”, “antidiabetic prescribing trends”, “patterns”, “trends”, “prescription rate”, “antidiabetic prescribing trends”, “prescription”, “medication”, “medicine”, “drugs”. The searches were limited to English language to ensure only peer reviewed articles were included in the review. The results of the searches were managed in Endnote version X8 where duplicates were eliminated. Study titles and abstracts were screened and assessed independently by SR and ZB. The disagreements were resolved through discussion, and if this was not reached second supervisor (PT) was consulted. The full-texts of the potentially relevant articles were retrieved through the university’s library database, Summon. The papers cited in the reference lists of these articles were also scanned for additional articles which could be relevant to this review. SR and one supervisor (ZB) independently selected articles for further review based on predefined inclusion and exclusion criteria (table 2.1).

2.3.2.2 Type of participants

The criteria for the selected studies was that participants were 18 years old or older and were included regardless of gender. Studies were also included of the patient had a diagnosis code for T2D according to the International Classification of Diseases (ICD) or the study explicitly stated that the included

patients were diagnosed with T2D. Studies involving patients diagnosed with type 1 diabetes or unclear diabetes status were excluded as the clinical treatment of the two patient groups is not the same (Diabetes UK, n.d.).

Table 2.1 Study inclusion and exclusion criteria.

No.	Category	Inclusion criteria
1	Language of publication	English.
2	Year of publication	January 2000 to September 2017.
3	Publication type	Full-text articles discussing changes in prescribing of antidiabetic medicines.
4	Outcome measures	Retrospective studies measuring overall use of antidiabetic medicines, antidiabetic medicines used at treatment initiation, prescription rate.
5	Methodology	Studies included must demonstrate use of antidiabetic medicines by using primary care databases.
6	Prescribing trends	Changes in use of antidiabetic medicines must play the significant or integral role when multiple outcomes were presented.
7	Type of diabetes	Type 2 diabetes mellitus only.
8	Patients	Adults prescribed oral antidiabetic medicines (OADs) or insulin in primary care.
No.	**Category**	**Exclusion criteria**
1	Language of publication	Published in other than English.
2	Year of publication	Published before January 2000 and after September 2017.
3	Publication type	Abstracts, reports, commentaries, editorials, book chapters, systematic reviews, meta-analysis.
4	Outcome measures	Studies on pregnant women.
5	Outcome measures	studies on elderly.
6	Outcome measures	Studies with focus on a specific drug class.
7	Outcome measures	Studies that does not consider type of diabetes.
8	Outcome measures	Studies with both in- and outpatient data.
9	Outcome measures	Studies without relevant outcomes e.g. switching medicine.
10	Outcome measures	Studies with focus on patients.
11	Outcome measures	Studies conducted in hospitals and clinics.
12	Outcome measures	Studies on children.

2.3.2.3 Outcome measures

Peer-reviewed articles published on changes in prescribing trends across the globe were included. Papers were included if they reported on: 1) overall use of antidiabetic medicines, 2) antidiabetic medicines used as treatment initiation and 3) prescription rate of antidiabetic medicines. In those articles where multiple outcomes were presented, the article was included if changes in the use of antidiabetic played a significant or integral role. Articles were excluded if they focused on children, pregnant women, elderly, a specific drug class, did not differentiate between type of diabetes, included data on in-and outpatients, conducted in hospital and clinics, focused on patients and studies without relevant outcomes e.g. switching medicines. Additionally, abstracts, reports, commentaries, editorials, journalistic articles, book chapters, systematic reviews and meta-analyses were excluded.

2.3.2.4 Assessment of risk of bias

The risk of bias of each eligible study was assessed by SR and discussed with ZB and PT until consensus was achieved. The methodological quality of the included articles were assessed using the Newcastle–Ottawa Scale (Wells et al., 2000). The methodological quality of the studies was not used as criterion for inclusion in the study.

2.3.2.5 Data extraction

The articles were screened and chosen by SR and discussed or checked by ZB and PT as indicated in each sub-section above.

2.3.2.6 Data synthesis

The 27-item PRISMA checklist was adopted and attached as appendix 1. The main findings from all reviewed studies were collated in Microsoft Excel version 2016 workbook. The main themes included were study design, study participants and setting, eligibility criteria, sample size, described trends and statistical methods.

2.3.3 Findings

2.3.3.1 Study characteristics

In this systematic literature review 12,467 articles were retrieved from the searched databases and hand-screening of articles. The retrieved articles were screened against the predefined inclusion and exclusion criteria and organised as shown in figure 2.1.

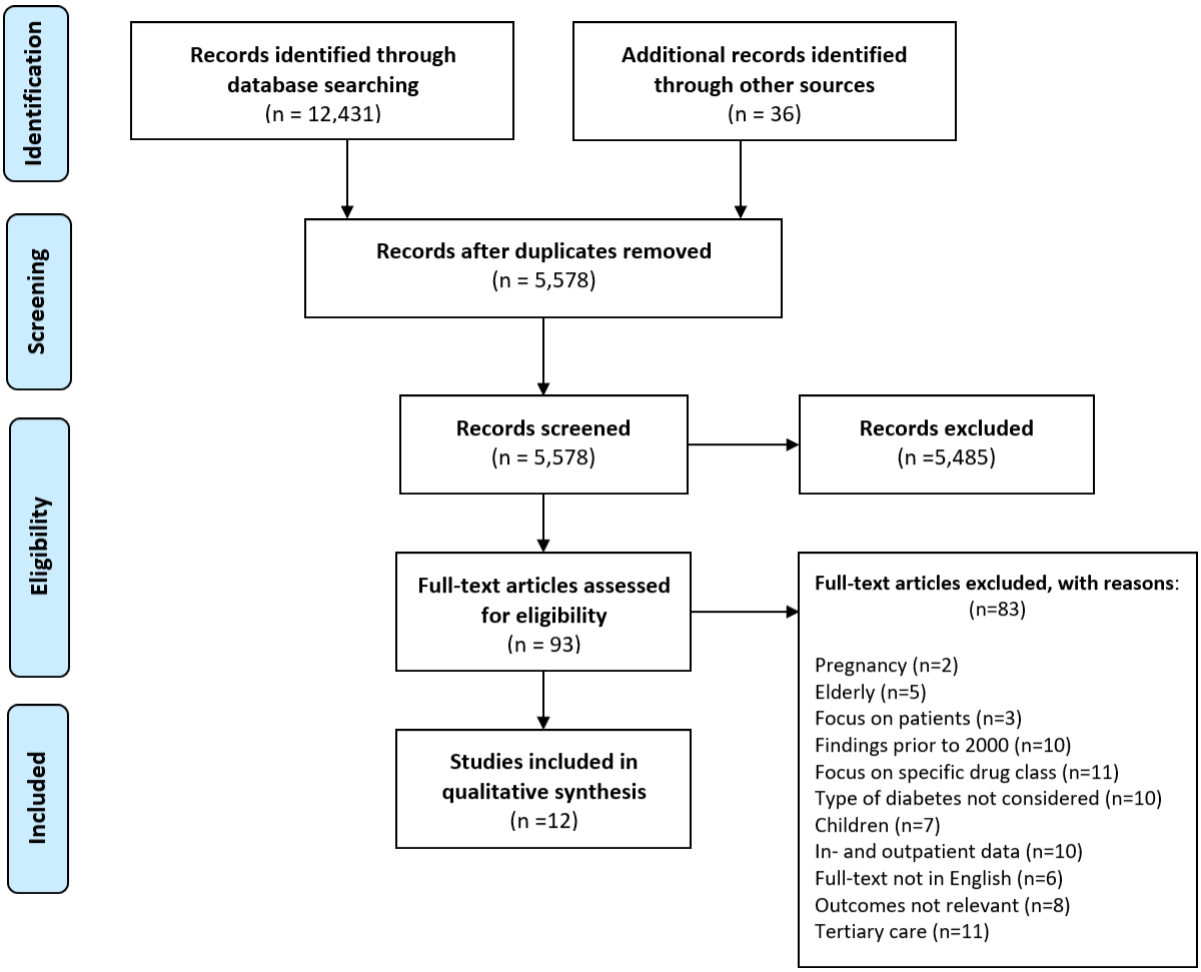


Figure 2.1 Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram.

Twelve original research articles met all inclusion criteria and were included in this review (Boyc, Yurgin, & Lage, 2007; Datta-Nemdharry, Thomson, Beynon, & Donegan, 2017; Filion, Joseph, Boivin, Suissa, & Brophy, 2009; Geier et al., 2014; Maguire, Mitchell, & Ruzafa, 2014; Mata-Cases, Franch-Nadal, Real, & Mauricio, 2016b; Mata-Cases et al., 2014; Overbeek et al., 2017; Sharma, Nazareth, & Petersen, 2016; Wilkinson et al., 2018; Willey, Andrade, Cohen, Fuller, & Gurwitz, 2006; Yurgin, Secnik, & Lage, 2007). The findings of prescribing trends from the systematic literature review were organised into the following two themes: *1)* overall prescribing trends of antidiabetic drug classes and *2)* prescribing trends of antidiabetic drug classes during treatment initiation.

2.3.3.2 Critical appraisal

Table 2.2 summarises the quality score assigned to each article. The scores ranged between 4 and 7. It was noted that the main reason for loss of score was that response was not included in the study.

Table 2.2 Quality assessment score of the reviewed articles

Author, year	Selection				Comparability	Outcome		
	1	2	3	4	5	6	7	Total
Boyc, 2007	⊕	⊕	Ø	⊕	⊕⊕	⊕	⊕	7
Datta-Nemdharry, 2017	⊕	⊕	Ø	⊕	⊕⊕	⊕	⊕	7
Filion, 2009	⊕	⊕	Ø	⊕	⊕	⊕	⊗	4
Geier, 2014	⊕	⊕	Ø	⊕	⊕	⊕	⊕	6
Maguire, 2014	⊕	⊕	Ø	⊕	⊕⊕	⊕	⊕	7
Mata-cases, 2014	⊕	⊕	Ø	⊕	⊕⊕	⊕	⊕	7
Mata-cases, 2016	⊕	⊕	⊕	⊕	⊕⊕	⊕	⊕	8
Overbeek, 2017	⊕	⊕	Ø	⊕	⊕⊕	⊕	⊕	7
Sharma, 2016	⊕	⊕	Ø	⊕	⊕⊕	⊕	⊕	7
Willey, 2006	Ø	⊗	Ø	⊕	⊕⊕	⊕	⊕	5
Yurgin, 2007	⊕	⊕	Ø	⊕	⊕	⊕	⊕	6
Wilkinson, 2018	⊕	⊕	Ø	⊕	⊕	⊕	⊕	6

*In each category maximum number of points which can be given are: Selection (1), Comparability (2) and Outcome (1).
**Explanation of symbols: ⊕ = + 1 point; ⊗ = – 1 point; Ø = 0 points

2.3.3.3 Study characteristics

The papers which met all the inclusion criteria described prescribing trends in France (n=2), England and Wales (n=1), UK (n=5), Germany (n=2), Spain (n=3), Netherlands (n=1), Italy (n=1) and United States of America (n=1). The study published by Overbeek and colleagues (Overbeek et al., 2017), was the only study collecting data from more than one country. The study characteristics have also been summarised in table 2.3. For the ease of contrast and comparison, prescribing trends have been

summarised as text only and presented drug by drug. For papers with multiple outcomes, only those outcomes relevant to current systematic literature review have been included.

Table 2.3 Study characteristics.

Author, country	Study design	Study Duration (years)	Sample (n)	Age (years)	Males (%)	Defined eligibility criteria for T2D *	Described trends	Outcome measure	Statistical method
France (Boyc et al., 2007)	Cross-sectional cohort, Retrospective primary care database analyses	2Y (2001-2003)	14,281	≥20	57	Categorized as having T2D over the calendar year 2001, 2002 or 20003 Must be categorised with [ICD]-10 code of E11 Alternative criteria listed	Prevalence of antidiabetic medicines prescribing	Changes in prescribing trend over study period Odds Ratios for the Likelihood of treatment	Univariate analysis Multivariate logistic regression Cochrane- Armitage test
England and Wales (Datta-Nemdharry et al., 2017)	Sectional cohort, Retrospective primary care database analyses	12Y (2000-2012)	123,671	≥18	56	At least one year of follow-up prior to cohort entry New patients were eligible f their first record had specific diagnosis of T2D or non-specific diabetes diagnosis (non-insulin users)	Treatment initiation	Changes in prescribing trend over study period	Descriptive analysis, Kaplan-meier estimates
United Kingdom (Filion et al., 2009)	Sectional cohort, Retrospective primary care database analyses	6Y (2000-2006)	67,981	≥30	55	Presence of a clinical diagnosis od T2D HbA1c ≥7% or ≥2 prescriptions for antidiabetic medicines	Prescription rates	Changes in prescribing trend over study period	Descriptive analysis
Germany (Geier et al., 2014)	Sectional cohort, Retrospective primary care database analyses	6Y (2003-2009)	27,138	≥40	49	T2D First time users of antidiabetic medicines Had not been treated with antidiabetics in the six months prior to enrolment to disease management program	Treatment initiation	Changes in prescribing trend over study period	Multivariable logistic regression model
United Kingdom (Maguire et al., 2014)	Sectional cohort, Retrospective primary care database analyses	5Y (2006-2010)	63,060	-	57	T2D First time users of antidiabetic medicines	Treatment initiation	Changes in prescribing trend over study period	Multinominal logistic regression
Spain (Mata-Cases et al., 2014)	Sectional cohort, Retrospective primary care database analyses	1Y (2009)	286,791	≥31	53.7	Diagnosis of T2D [ICD]-10 of E11 or E14 Individual was considered in treatment when they obtained ≥80% of the theoretical minimum dose from the first to last prescription in 2009	Prevalence of antidiabetic medicines	Changes in prescribing trend over study period	Descriptive analysis, Pearson chi-square tests, multilevel logistic regression model

Spain (Mata-Cases et al., 2016b)	Sectional cohort, Retrospective primary care database analyses	7Y (2007-2013)	343,969[1]	≥31	68.9[1]	Diagnosis of T2D [ICD]-10 of E11 or E14	Prevalence of antidiabetic medicines	Changes in prescribing trend over study period	Descriptive analysis
Netherland Spain United kingdom Italy France (Overbeek et al., 2017)	Retrospective primary care database analyses	5Y (2008-2012)	253,530	-	52	Diagnostic code for diabetes Or received at least 2 prescriptions doe an oral antidiabetic medicine	Prevalence of antidiabetic medicines	Changes in prescribing trend over study period	Descriptive analysis
United Kingdom (Sharma et al., 2016)	Sectional cohort, Retrospective primary care database analyses	13Y (2000-2013)	406,344	≥0	-	At least two of the following criteria were met: a) Diagnostic code for diabetes b) supporting evidence for diabetes c) treatment for diabetes	Prevalence of antidiabetic medicines prescribing Treatment initiation	Changes in prescribing trend over study period	Multivariable Poisson regression analysis, Likelihood-ratio tests
United States of America (Willey et al., 2006)	Retrospective, HMO automated database	1Y (2002)	4,282	≥18	54	Diagnostic code for T2D, [ICD-9CM] Additional, continuous enrolment in the staff-model component	Treatment initiation	Changes in prescribing trend over study period	Descriptive analysis, logistic regression likelihood-ratio tests
Germany (Yurgin et al., 2007)	Sectional cohort, Retrospective primary care database analyses	1Y (2004)	5,135	≥20	52.6	Diagnosis of T2D [ICD]-10 of E11 or E14 Diagnosis of T2D [ICD]-10 of E12, E13 or E14 and had received at least 2 prescriptions an oral antidiabetic medicine and not received diagnosis of type 1 diabetes mellitus	Treatment initiation	Changes in prescribing trend over study period	T tests, χ^2 tests
United Kingdom (Wilkinson et al., 2018)	Retrospective primary care database analyses	18Y (2000-2017)	280,241	≥18	-	Participant must be registered with a general practice recording research quality data for a period of 12 months before starting drug treatment for diabetes Excluded women with a record of pregnancy T2D drugs were identified based on British National Formulary T2D chapters	Treatment initiation	Changes in prescribing trend over study period	Descriptive analysis

*Other study specific criteria such as duration of prescriptions received are not mentioned here.

2.3.3.4 Overall prescribing trends of antidiabetic drug classes

In the follow section a descriptive summary of the overall prescribing trends of antidiabetic medicines drug classes have been described as percentage of all antidiabetic medicines.

Metformin

In a study conducted in France (2001 to 2003), the prescribing of metformin was reported to increase from 17% to 21% (Boyc et al., 2007). Yurgin and colleagues (2004) reported that about 20% of patients in Germany were prescribed metformin (Yurgin et al., 2007). In a study conducted in Spain in 2014, the prescribing of metformin was reported to be 40 % (Mata-Cases et al., 2014). Two studies which were conducted in the UK during an overlapping time period reported prescribing of metformin to be 91% and 90.7%, respectively (Maguire et al., 2014; Sharma et al., 2016). Similarly other studies conducted in the UK and Spain (Filion et al., 2009; Mata-Cases et al., 2016b) during the same time period (2000-2006 and 2007-2013) also reported an increase in the rate of metformin prescriptions.

Sulfonylurea

Sulfonylurea was reported as the most commonly prescribed drug class in France (Boyc et al., 2007). During the study period (2001-2003) there was an observed decline in prescribing from 35% to 29%. A study conducted by (Overbeek et al., 2017) across five European countries (2008-2012) showed a similar prescribing trend. This study found sulfonylurea to be the second most commonly prescribed drug class. In other European studies (2009 and 2004) the prescribing trend was observed to be 12% and 17% of patients, respectively (Yurgin et al., 2007). In a UK based study (2000-2006) a similar decrease was observed in the prescribing trend. Lastly, a study conducted by Mata-Cases (Mata-Cases et al., 2016b) in Spain reported a reduction from 34% to 26% in the prescribing rate of sulfonylurea.

Thiazolidinediones

It was evident from the reviewed articles that the use of thiazolidinediones increased rapidly as soon as it became available on the market in each country. Fillion et al. reported a rapid uptake in the prescribing of thiazolidinediones of the drug class between 2000 and 2006 (Filion et al., 2009). Sharma et al. reported the use to be about 8% with a peak in 2007 (Sharma et al., 2016). The study by Overbeek and colleagues (Overbeek et al., 2017) reported a decline in the use of thiazolidinediones in the Netherlands, Spain and France. In France it was reported that the use of thiazolidinediones as monotherapy was completely withdrawn in 2011. In Germany the use of thiazolidinediones was reported to be less than 1% in 2004 (Yurgin et al., 2007).

Dipeptidyl peptidase-4 inhibitors

The prescribing of dipeptidyl peptidase-4 inhibitors (DPP-4i) was reported to vary across the countries. The prescribing was reported to increase from 0% to 27% in France, <1% to 9% in the UK and from 0% to 9% in Spain (Overbeek et al., 2017). In the same study, it was reported that prescribing remained low in the Netherlands and Italy where it was 4% and 2%, respectively. The authors of a study conducted in Spain reported an increase in prescribing of 13% between 2007 and 2013 (Mata-Cases et al., 2016b).

Insulin

Insulin monotherapy prescribing was reported to increase from 1.71% 2.27% in France over a period of three years (2001-2003) (Boyc et al., 2007). In Germany, prescribing was reported as 11% (2004) and 8% (2014) in Spain (Mata-Cases et al., 2014; Yurgin et al., 2007). Findings in the UK were varying as one study reported a stable number (2000-2013) of insulin prescriptions, while the other study reported a 10% (2000 to 2006) increase in the rate of insulin prescriptions (Filion et al., 2009; Sharma et al., 2016).

Other antidiabetic drug classes

Glucagon-like peptide 1 receptor agonists (GLP-1RA) prescribing was reported to increase in France and the UK (Overbeek et al., 2017). The Netherlands, Italy and Spain reported a decline in prescribing of GLP-1RA (Overbeek et al., 2017). In Spain, it was reported that GLP-1RA prescribing had increased from 0% to 1% between 2007 and 2013(Mata-Cases et al., 2016b).

2.3.3.5 Prescribing trends of antidiabetic drug classes during treatment initiation

Metformin

Six studies reported on the use of metformin during treatment initiation. One study conducted in England and Wales (2000 to 2012) reported 80% of patients to be initiated on metformin (Datta-Nemdharry et al., 2017). In another study conducted during an overlapping time period in the UK (2000-2017), the prescribing of metformin during treatment initiation was reported as 73% (Wilkinson et al., 2018). Other studies reported an increase in the use of metformin monotherapy during treatment initiation. The prescribing was reported to increase from 63% to 80% in Germany (2003 to 2009) (Geier et al., 2014), 84% to 91% in UK (2006 to 2010) (Maguire et al., 2014) and 45% to 91% in another UK based study (2000 to 2013) (Sharma et al., 2016).

Insulin

In a study conducted in England and Wales(2000 to 2012), twelve percent of the patients were reported to have received insulin during treatment initiation (Datta-Nemdharry et al., 2017). Another study conducted in the UK during an overlapping time period (2006 to 2010) reported a decrease in insulin prescribing at treatment initiation from 10% to 2% (Maguire et al., 2014). A third UK study reported a similar low prescribing frequency of 1.7% (Sharma et al., 2016). Similarly a UK study conducted between 2000 and 2017 reported an overall insulin prescribing of 2%(Wilkinson et al., 2018).

2.3.3.6 Overall prescribing trends of mono- and combination therapy

Overall, there was an increase in the number of patients treated with a combination of metformin and insulin. Simultaneously, there was a tendency towards a decrease in sulfonylurea prescribing. A study conducted in France by Boyc et al. showed a steady number of patients treated with two oral antidiabetic drug classes (55.79% to 54.65%). The number of patients treated with a combination of one oral antidiabetic drug plus insulin increased from 5.01% to 54.65%. The number of patients treated with a

combination of two oral antidiabetics plus insulin remained almost stable (1.71% to 1.35%). Likewise, the number of patients treated with triple therapy also increased (6.69% to 5.95%) (Boyc et al., 2007). Geier and colleagues (Geier et al., 2014) reported that the number of patients treated with monotherapy, oral combination therapy and oral antidiabetic medicine plus insulin to be 43%, 11% and 4%, respectively.

Geier et al. (Geier et al., 2014) reported combination therapy to be uncommon during treatment initiation. One study conducted in England and Wales showed about 2% of patients to be treated with a combination of sulfonylurea and metformin (Datta-Nemdharry et al., 2017). Only 0.12% of patients were reported to be treated with a combination of insulin plus another drug class during treatment initiation (Datta-Nemdharry et al., 2017). Another UK based study (Maguire et al., 2014) observed 0.2% of patients to be treated with a combination therapy and of these patients 85% received a combination of metformin and sulfonylurea.

2.3.4 Discussion

The scope of this systematic literature review was to evaluate the changes in the use of antidiabetic medicines prescribed to treat T2D in primary care settings. It was evident from previous research that there has been an increase in the overall use of antidiabetic drugs (Christensen, Rungby, & Thomsen, 2016; Filion et al., 2009; Ko et al., 2016). At the same time, there has been significant changes in the prescription pattern of antidiabetic drugs. These changes in prescription patterns are marked by the introduction of the new drug classes such as thiazolidinediones, DDP-4i, GLP-1RA and sodium-glucose co-transporter 2 inhibitors (SGLT-2i). Due to the availability of new scientific evidence on these drug classes as well as changes or updates in national and international prescribing recommendations. These changes happened at different times across the surveyed countries and was dependent on the availability of drugs and changes in prescribing recommendations in each specific country.

The increase in the number of patients treated with metformin and the decline in the prescribing of sulfonylurea reflect the update of national T2D guidelines such as in the UK and Denmark (NICE, 2015; Sundhedsstyrelsen, 2019) and other international T2D prescribing guidelines (American Diabetes Association, 2018a; Inzucchi et al., 2015). A number of studies recognised that although metformin monotherapy had been available for years, the first publication and updates of the United Kingdom Prospective Diabetes Study (UKPDS) over the years has contributed to the recognition of the drug as being efficient in bringing down HbA1c levels among patients(UKPDS, 1998b). The first UKPDS study was published in 1998 and followed patients over a three year period (UKPDS, 1998b). The study showed significant improvement in HbA1c levels when metformin was added to sulfonylurea at an early stage of treatment. Soon after the publication of the UKPDS study an increasing number of national and international guidelines started to recommend metformin as first-line treatment. Other factors includes the launch of metformin as a new entity in the US market (Alexander, Sehgal, Moloney, & Stafford, 2008) and publication of 10-year data UKPDS data at the EASD Conference in Barcelona (UKPDS, 2017).

The global prescribing trend shows that thiazolidinedione prescribing picked up as soon as they became available, however the prescribing of the drug class reached its peak around 2007/2008. However, troglitazone was withdrawn from the US market due to the report of hepatoxicity (Mitchell, 1997). Another two drugs within this drug class were launched, rosiglitazone and pioglitazone. However the safety profiles of these two drugs means they are not suitable for all patients (EMA, 2011; Food and Drug Administration, 2007; Hurren, Taylor, & Jaber, 2011). This was also reflected in the recommendations in national and international guidelines at the time which favoured other drugs classes which fewer adverse events (Nathan et al., 2008; NICE, 2008).

Dipeptidyl peptidase-4 inhibitors (DDP-4i) were introduced around the time where the safety concerns regarding thiazolidinediones peaked and hence it became a popular alternative for patients for whom rosiglitazone and pioglitazone were not suitable. The literature suggests that this was also the reason the prescribing picked up soon after its launch on the market (Kohro et al., 2013).The findings of this review reflect the current international prescribing guidance which recommends the use of DDP-4i as second or third-line drug therapy (Davies et al., 2018; NICE, 2015).

The overall prescribing frequency of insulin varied across the surveyed countries. However, the majority of the surveyed studies found an increase in prescribing. The increase in the use of insulin can be explained by the availability of new long acting insulin (Boyc et al., 2007; Hilgenfeld, Seipke, Berchtold, & Owens, 2014; Ko et al., 2016). The introduction of long acting insulin was a step forward in the treatment with injectables as this was much needed in clinical settings.

International diabetes guidelines were promoting more intensive glucose control as early introduction of tight glycaemic control was found to have a lasting effect (Bianchi, Daniele, Dardano, Miccoli, & Del Prato, 2017). However, the current guidelines do not have set recommendation for when insulin treatment should be initiated (IDF, 2012; Inzucchi et al., 2015). Both consultant and primary care healthcare professionals are left to use their own clinical judgement to decide when insulin treatment should be initiated (Al Khaja, Sequeira, & Damanhori, 2005; P. Home et al., 2014). The current trend is to initiate insulin treatment after trialling between two and four drugs without achieving the desired outcomes. The evidence shows that the decision to delay is often a choice of the clinician rather than the patients (Peyrot et al., 2005). Furthermore, the presentation of disease at an earlier age means that the patients are under treatment for a longer time which is also another factor toward increase in the usage of insulin (P. Home et al., 2014). The overall prescribing trend of GLP-1RA described across the studies varied, however the prescribing frequency was reported to be very low. Among the reviewed papers, there were not any significant reports on the prescribing of SGLT-2i. Limited reporting on use of GLP-1RA and SGLT-2i can be explained as the first medicines in each drug class was launched in 2007 and 2013, respectively. This also means that the clinical trial outcomes on these two drug classes keep changing. GLP-1RA are found efficient to bring cardiovascular and mortality rates down (Bethel et al., 2018). SGLT-2i also have shown promising results in clinical trials where they have shown to reduce events of hospitalisation for heart failure events and cardiovascular mortalities (Norhammar et al., 2019; Wiviott et al., 2018).

2.3.5 Limitations

It was the goal of this systematic literature review to review the evidence on use of antidiabetic medicines in a global context. The findings should be seen in context of the applied inclusion and exclusion criteria mind. As this review set out to look at prescribing patterns in primary care, the findings are not necessarily reflective of the prescribing pattern in secondary care. It is estimated that 90 % of patients with T2D are treated in primary care (WHO, 2013). It was noted that the reviewed studies did not report on the use lifestyle interventions and drugs used to treat comorbidities related to T2D. It is also important to mention the methodological difference between the reviewed studies. Most studies in this review classified to have T2D if they had the ICD-code for this whereas other studies considered a patient to have T2D if they had bought antidiabetics at least once in the year. Moreover, because of the structure of the published data, there is limited knowledge regarding how many patients were treated with diet and lifestyle changes.

2.3.6 Conclusion

This systematic literature review sought to review changes in use of antidiabetic medicines. The findings from this review show that the launch of new drug classes on the market was reflected in the choice of drug classes being prescribed in primary care. This review for instance showed a change in the use of metformin as first-line treatment initiation has superseded the use of sulfonylurea as first-line treatment during the observation period. The changes in prescribing patterns is suggested to be a result of change in the national and international prescribing guidelines in the surveyed countries. The usage pattern of antidiabetic medicines also showed that the reporting of unwanted side-effects and withdrawal of drug classes from the market had a negative impact on the use of drug classes. This was for instance seen in the increase and decrease in the use of newer drug classes such as thiazolidinediones, DDP-4i and GLP-1RA. Metformin and insulin are the most frequently mentioned drug classes used during treatment initiation.

2.4 Part III: Cost of antidiabetic medicines

2.4.1 Aim and objective

The aim of this systematic literature review was to synthesize evidence on cost of antidiabetic medicines and compare the expenditure across economically developed countries.

2.4.2 Methods

2.4.2.1 Search strategy

For the purpose of this review PubMed, EMBASE, CINAHL, Cochrane Database of Systematic Reviews, and Springer Link were searched for relevant peer reviewed research papers. The following keywords were systematically searched in combination in each of the databases: “pharmaceuticals” (e.g. cost, costs, expenditure), “medicines” (e.g. drug, drugs, glucose lowering drugs, medications, medicine or medicines), “diabetes” (e.g. type 2 diabetes, type 2 diabetes mellitus, or hypoglycaemia) and “economics” (e.g. direct cost, hospitalisation, service cost, cost of illness, or health care cost). Further, the articles included in this review was selected based on the pre-defined inclusion and exclusion criteria (table 2.4). The search was limited to include articles published in English language between 2007 and 2017. The country should be classified as upper middle income or high income country as per definition of the World Bank (The World Bank, n.d.). The search findings were managed in Endnote software, where duplicates also were eliminated. Titles and abstracts of eligible studies were screened and assessed independently by SR and one supervisor (ZB). In case of disagreement after discussion, second supervisor (PT) was consulted. The university’s library database, Summon was used to retrieve all relevant full-text articles. The reference lists of these articles were hand screened to identify other articles with relevance to this review.

Table 2.4 Inclusion and exclusion criteria

Inclusion criteria
• Published between 2007 to 2017. • English language. • Studies that consider diabetes from individuals the health services or society perspective. • Upper middle income or high income country as per definition of the World Bank (The World Bank, n.d.).
Exclusion criteria
• Studies that does not quote costs in results section. • Studies on adherence. • Studies on the saving on using one drug class instead of other. • Studies on comorbidities e.g. chronic kidney disease, heart conditions, obesity/lifestyle interventions. • Studies that do not differentiate between diabetes status. • Studies that consider diabetic complications e.g. diabetes foot, diabetic nephropathy. • Cost-effectiveness, cost-utility and cost minimisation studies. • Studies on developing countries. • Conference abstracts, reviews, book etc. • Diabetes with other co-morbidities (e.g. heart condition). • Pharmacodynamics and pharmacokinetic studies. • Animal and in vitro studies.

2.4.2.2 Type of participants

The studies included in this review had explicitly stated that the patients had a confirmed diagnosis of T2D.

2.4.2.3 Outcome measures

The research papers were included in the review if they evaluated the direct cost of T2D and cost of antidiabetic medicines. The articles were excluded from the review if their main focus was to: *1)* to evaluate on policy changes of cost of medicines, *2)* reported on cost of complications related to T2D, *3)* reported on cost of comorbidities related to T2D*, 4)* did not distinguish between type 1 diabetes and T2D, *5)* did not assess outcomes relevant to this review, and *6)* did not report on original data. A complete list of reasons for exclusion from the review is provided in table 3.4. Additionally, abstracts, reports, commentaries, editorials, book chapters, systematic reviews and meta-analyses were excluded from this systematic literature review.

2.4.2.4 Assessment of risk of bias

The applied quality assessment tool was adapted from previous systematic literature review of quantitative studies (Louw, Morris, & Grimmer-Somers, 2007; Roman, 2013; Wong, Cheung, & Hart, 2008). The study score of each eligible study was calculated by SR and checked by ZB. The studies were scored according to reported response of each domain. No response or non-report would lead to score of 0 and a reported response would lead to score of 1. The tool assessed the quality of the studies based on quality assessment items (e.g. response rate and applied tools) and relevance to current review (e.g. outcome measurements and study questions). The quality rating of each item was evaluated on a "poor", "fair" and "good" basis. The studies that scored from 0%–33.9% were considered weak, 34%–66.9% were considered moderate, and 67%–100% were interpreted as strong.

The study score of each article has been presented in table 2.5. The studies were also assessed to score "strong" on the quality appraisal tool.

2.4.2.5 Data extraction

SR and one supervisor (ZB) independently selected articles for further review and this was based on the predefined inclusion and exclusion criteria.

2.4.2.6 Data synthesis

The PRISMA checklist (appendix 2) was adopted and used for this systematic literature review . The main outcomes from all reviewed studies were collated in a Microsoft Excel workbook and tabulated.

Table 2.5 Quality appraisal score of each eligible study [a, b].).

Study	Quality assessment items					Relevance to current review			
	A	B	C	D	E	F	G	H	Score %
(Bahia et al., 2011)	1	1	1	1	1	1	1	1	100 %
(Borges, Ferraz, & Chacra, 2014)	1	1	1	1	1	1	1	1	100 %
(Demurtas et al., 2017)	1	1	1	1	1	1	1	1	100 %
(Domeikienė, Vaivadaitė, Ivanauskienė, & Padaiga, 2014)	1	1	1	1	1	1	1	1	100 %
(Elgart et al., 2014)	1	1	1	1	1	1	1	1	100 %
(Jacob, von Vultee, & Kostev, 2017)	1	1	1	1	1	0	1	1	87.5 %
(Mata-Cases et al., 2016a)	1	1	1	1	1	1	1	1	100 %
(Ng, Toh, Ko, & Lee, 2015)	1	1	1	1	1	1	1	1	100 %
(Ulrich et al., 2016)	1	1	1	1	1	1	1	1	100 %

[a] *Score:* total score divided by the total number of items multiplied by 100
[b] *Quality appraisal score and match with the objectives of current review*: Weak - 0-33.9%; Moderate - : 34-66.9%; Strong - 67-100%

***Abbreviations:* 0 - No/not reported; 1 - Yes; A - Was the sample likely to be representative of the study population?; B - Was a response rate mentioned within the study?; C - Was the instrument used reliable?; D - Was the instrument used valid? E - Was it a primary data source? F – Does study evaluate on direct cost used to treat type 2 diabetes?; G – Does study evaluate on cost of medicines used to treat type 2 diabetes?; H – Does the patient have unambiguous diagnosis of T2D?**

The study characteristics of the reviewed studies included study design (e.g. cohort, cross-sectional, bottom up approach), sample size (number of patients diagnosed with T2D), data source (e.g. medical charts, interviews and questionnaires) and inclusion criteria (e.g. diagnosis codes used). The main themes from the reviewed articles have been organised into categories: *1)* mean annual direct cost, *2)* mean annual antidiabetic medicine cost, *3)* items included in the estimation for direct cost, and *4)* antidiabetic medicines included medicine cost (where possible cost of medicines for other conditions than diabetes have been excluded).

Based on the reported cost estimates the *mean annual cost* was calculated. Where the reported currency was expressed in another currency than US dollars the currency was converted to US dollars (box 3.1: calculation example 1). Then, all reported cost estimates were calculated to express the corresponding 2017 values for US dollars (box 2.1: calculation example 2). A two percent inflation rate was used for these calculations (Barua, 2017). The exchange rate adopted in this study was 1 US$ = 1.998 and 1 US$ = 0.0537 AR$, as per average exchange rate reported on December 31st 2017 (Yahoo, n.d.). Where cost for both private and public tariffs were available it was preferred to use (1) average costs and where not available (2) public tariff.

Box 2.1 Examples of cost calculation of mean annual cost to US dollars 2017 values.

Calculation example 1: Calculation of future value when reported currency is different from US dollars:

$C = (1 + r)^n$

,where C = future value, r = inflation (2%), and n = number of years since 2017

Northern Italy future value = $3{,}312€ * (1 + 0.02)^7 = 3{,}803.89€ \sim 3{,}800€$

Euros are now converted to US dollars. Exchange rate for last day of the year (31/12/2017) has been found to be 1.998.

Mean value expressed in 2017 dollars: $3803.89€ * 1.998 =$ **7,600.18$**

Calculation example 2: Calculation of future value when currency is reported in US dollars:

$C = (1 + r)$

,where C = future value, r = inflation (2%), and n = number of years since 2017

Brazil future value: $1{,}335\$ * (1+0.02)^{12} = 1{,}718.47\$ \sim$ **1,720$**

2.4.3 Findings

2.4.3.1 Study characteristics

During this systematic literature review 525 peer reviewed articles were identified to be eligible for title/abstract screening (*see figure 2.2 for flowchart*). Out of 525, 34 articles met the inclusion criteria after reviewing titles and abstracts. After reviewing full-texts nine articles were found to meet all the predefined inclusion and exclusion criteria (Bahia et al., 2011; Borges et al., 2014; Demurtas et al., 2017; Domeikienė et al., 2014; Elgart et al., 2014; Jacob et al., 2017; Mata-Cases et al., 2016a; Ng et al., 2015; Ulrich et al., 2016). The studies included in this review were from Brazil (n=2), Northern Italy (n=1), Lithuania (n=1), Argentina (n=1), Spain (n=1), Singapore (n=1) and Germany (n=2).

The studies were conducted in primary care, secondary care or tertiary care. On average it was found that more females than males were included in the studies. The mean age of the patients in the studies ranged between 59 and 71 years. All participants had a diagnosis of T2D. Four studies (Bahia et al., 2011; Borges et al., 2014; Jacob et al., 2017; Ulrich et al., 2016) identified patients to have T2D without further specification of the used ICD-9/ICD-10 codes to identify T2D patients (Domeikienė et al., 2014; Elgart et al., 2014; Mata-Cases et al., 2016a; Ulrich et al., 2016). One study (Demurtas et al., 2017) differentiated between type 1 diabetes and T2D by categorising antidiabetic medicines as “insulin treated diabetes” and “non- insulin treated diabetes”. All included studies reported on outcomes related to *direct cost* and *antidiabetic medicine cost*s of health care. It was noticed that there was not a standardised method of reporting the direct cost as the included components varied across the studies. The included components of each study are reported in table 2.6.

2.4.3.2 Main outcomes

A summary of the direct cost of T2D and the cost of diabetes mellitus medicines has been presented in table 2.7. The medicines cost estimates were categorised as follows: *1)* diabetes and obesity, *2)* antidiabetics/ glucose lowering drugs, *3)* no explanation of which medicines were included.

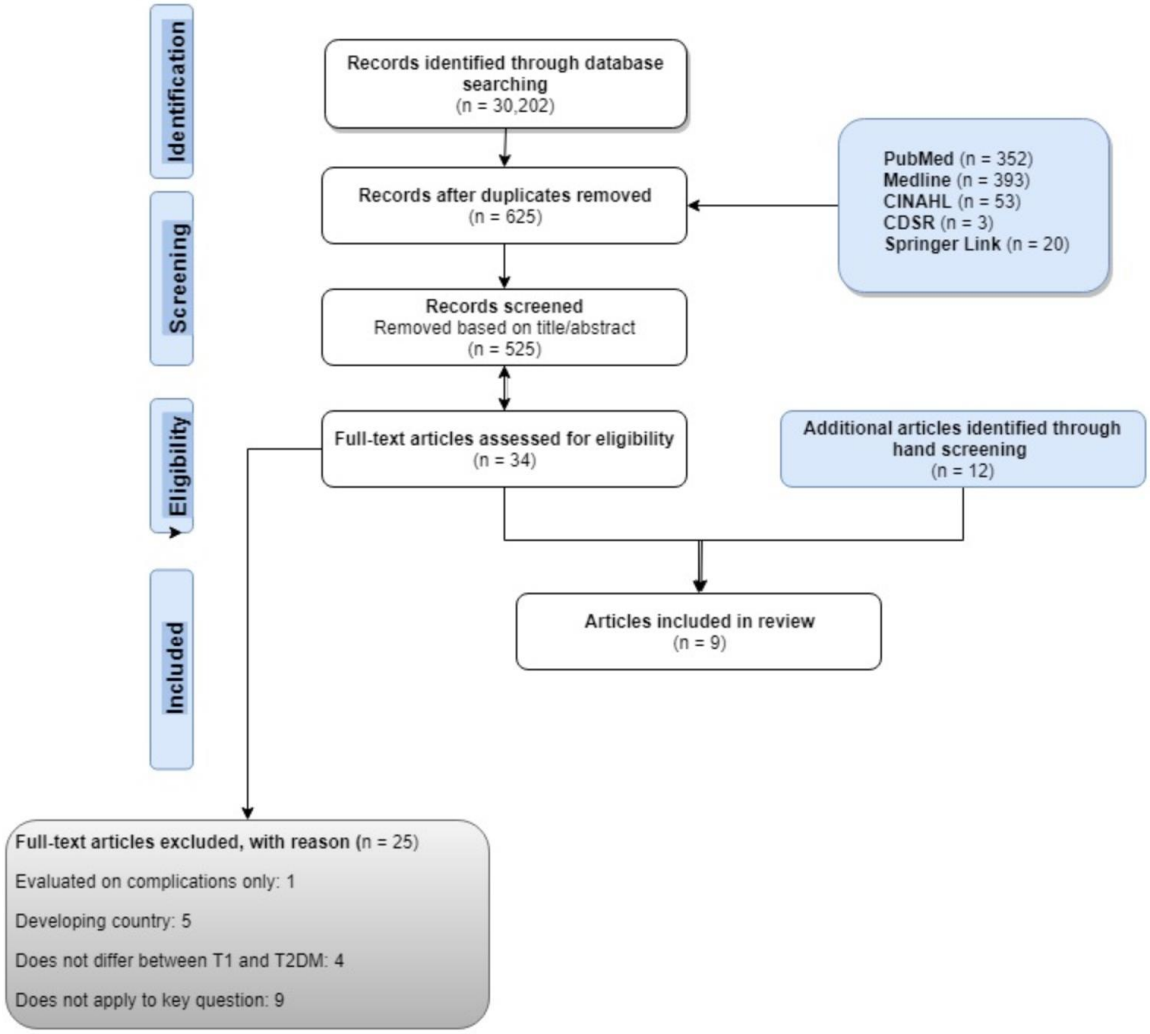


Figure 2.2 Flowchart depicting the selection process of articles included in the systematic review.

Table 2.6 Characteristics of included studies.

Country	Setting for study recruitment	Study design	Methods	Study duration (year)	Sample size (n)	Funding body	Inclusion criteria	Mean age (years)	Males (%)
Brazil (Bahia et al., 2011)	Primary, secondary and tertiary care units	Retrospective study	Questionnaire / interviews and Medical records	2007	1000	Publicly financed	Diagnosed T2D, no further specification	59	33.5
Brazil (Borges, Ferraz, & Chacra, 2014)	Diabetes care centre, tertiary care	Retrospective study	Interviews and reviews of medical charts, and questionnaires	2009-2010	209	Publicly financed	T2D patients over 18 and having regular follow-up consultations	63	42
Nothern Italy (Demurtas et al., 2017)	Tertiary sector	Retrospective study	Medical records	2012	24.087	Publicly financed	Diabetes classified as "insulin treated diabetes", and "non-insulin treated diabetes" above 45 years	69.2	52
Lithuana (Domeikiene, Vaivadaite, Ivanauskiene, & Padaiga, 2014)	Secondary care, ambulatory and hospital inpatient care	Top down approach	Medical records	2011	762	Publicly financed	T2D, ICD-10 diagnosis codes E11.0-9	67.07	37.7
Agentina (Elgart et al., 2014)	Secondary care, hospital care	Observational retrospective study	telephone interviews and medical records	2011	387	Publicly and privately financed	T2D, ICD-10	63	45
Germany (Jacob, von Vultee, & Kostev, 2017)	General practices and diabetic centres	Retrospective study	Medical records	2015	36382	Publicly and privately financed	Diagnosed T2D	N/A	52.2
Spain (Mata-Cases et al., 2016)	Primary care	Retrospective study	Medical records	2011	126811	Publicly financed	T2D, ICD-10 diagnosis codes E11, E14	67.5	53.5
Singapore (Ng, Toh, Ko, & Lee, 2015)	Hospital and clinic	Buttom up approach/ cross-sectional study	Medical records	2010	500	Publicly financed	T2D, ICD-9 code of 250	69	44.6
Germany (Ulrich et al., 2016)	Generel practitioner	Retrospective study	Questionnaires	2004-2012	6803	Publicly and privately financed	Diagnosed T2D, no further specification	71	54.1

Table 2.7 Cost of mean annual direct cost per person and mean annual medicine cost per person in the included studies.

Country	Price year	Currency/ exchange rate	Income group classification	Direct cost estimated on basis of following components	Mean annual direct cost per person	Mean annual direct cost per person expressed in US dollars 2017 [1,2]	Medication cost estimated on basis of	Mean annual antidiabetic medicine cost per person (% of total direct cost)	Mean annual medicine cost per person expressed in US dollars 2017 [1,2]
Brazil (Bahia et al., 2011)	2005	1 USD = 1.4 R$	Upper middle income	***Medications,*** diagnostic tests, procedures, medical supplies (such as blood glucose test strips), visits with health professionals (physicians, nurses, nutritionists, physical therapists, dentists, and psychologists), and hospital costs for emergency room visits (including provider fees only).	1,360	1,720	Medications used were categorized into four groups: ***diabetes and obesity***, cardiovascular and dyslipidemia, psychiatric, and others (all other classes of medications).	250 (18.38%)	320[2]
Brazil (Borges, Ferraz, & Chacra, 2014)	2009	$	Upper middle income	Procedures, hospitalizations, consultations, strips and tests/examinations and ***medications***.	1,000	1190	Medications was subdivided into four categories: ***antidiabetics, h***ypocholestero-linemics antihypertensives and others	440 (11.17%)	490
Nothern Italy (Demurtas et al., 2017)	2012	€	High income	Hospitalization, outpatient care cost, ***medications cost***	3.310	7,600	***Medications*** included: (meglitinides,non-sulfonylurea, sulfonylurea, thiazolidinediones, other antihyperglycaemic agents, long and short-acting insulins)	870 (26.40 %)	1000[2]
Lithuana (Domeikiene, Vaivadaite, Ivanauskiene, & Padaiga, 2014)	2011	1 EUR = 3.45 LTL	High income	Type of treatment, diabetes-related chronic complications (microvascular and macrovascular), consultations of general practitioners and specialists, laboratory tests, ***covered drugs and diabetes supplies***, ambulatory procedures, hospitalization, nursing services, healthcare at home costs	9560	2,150	Direct cost of drugs are subdivided into: ***Antidiabetic medication ,*** hypoglycaemic medication, Oral and non-insulin injectable hypoglycaemic medication, Oral hypoglycaemic medication and insulin, Insulin Diagnostics strips and Other medication	450 (44.91 %)	500
Argentina (Elgart et al., 2014)	2011	AR$	High income	***Medications*** (including out-of-pocket payment for prescribed drugs), laboratory tests and procedures, hospitalizations, medical and other associated health professional outpatient visits (consultations).	3,670	220	Does not differ between oral *medicines* used to treat T2DM w/o complications.	2,650[3] (72.33 %)	161

Germany (Jacob, von Vultee, & Kostev, 2017)	2015	€	High income	N/A	N/A	N/A	Nine different families of ***antihyperglycaemic therapy*** were included in the analysis. The annual antihyperglycaemic treatment cost per patient was calculated based on pharmacy retail prices.	500[4]	520
Spain (Mata-Cases et al., 2016)	2011	€	High income	Primary care visits (differentiating between doctor's or nurse's visits, and between place of visit, i.e., in the office or at home), hospitalizations, referrals to specialist care, diagnostic tests, ***medication***, dialysis treatment, and use of self-monitoring test strips.	3110	7,140	Does not differ between ***medicines*** used to treat T2DM. The retail prices were based on the pharmacy billing information.	930 (29.74 %)	1060
Singapore (Shuyu Ng, Toh, Ko, & Yu-Chia Lee, 2015)	2010	1 USD = 1.3 S$	High income	Inpatient hospitalisation, accident and emergency (A&E) and ambulatory outpatient care (physician visits, allied health visits, ***laboratory tests and medications***)	1,580	1,800	The cost of drugs other than **antidiabetics** were not included.	120 (7.97 %)	140
Germany (Ulrich et al., 2016)	2011	€	High income	Outpatient services, hospital care, ***rehabilitation and medication***	3350	7,540	Does not differ between ***medicines*** used to treat T2DM. Pharmaceutical expenditures were calculated from information on name, pharmaceutical identification number and dosage of drug intake during the previous 7 days. If pharmaceuticals were taken irregularly, the intake per week was assumed by using the defined daily dose (DDD).	960 (28.64 %)	1080

[1] Original values and calculations can be found in appendix 3
[2] Examples of calculations have been provided in the methods section
[3] Expressed during a 3-month period (90 days) in original paper
[4] Estimate for overall population

Six articles defined antidiabetic drug classes as "*antidiabetics"* (Bahia et al., 2011; Borges et al., 2014; Demurtas et al., 2017; Domeikienė et al., 2014; Jacob et al., 2017; Ng et al., 2015) and three articles used the term "*medicines used to treat T2D" (Elgart et al., 2014; Mata-Cases et al., 2016a; Ulrich et al., 2016).* The currency and price year of each included study have been converted to US dollars using exchange rates of December 31 2017. Currency, price year and examples of calculation provided in the original studies can be found in appendix 3.

The mean annual direct cost ranged between $220 per person (Argentina) and $7,600 per person (Northern Italy). The reported mean annual direct cost in the other European countries was quite similar; $7,140 per person in Spain (Mata-Cases et al., 2016a) and $7,540 per person in Germany (Ulrich et al., 2016). The two studies reporting data from Brazil has almost similar mean annual direct cost ($1,720 per person and $1,190 per person) (Bahia et al., 2011; Borges et al., 2014).

The mean annual medicine cost ranged between $140 per person (Singapore) and $1080 per person (Germany) . The reported mean annual medicine cost in the two studies conducted in Brazil were reported to be $320 per person (Bahia et al., 2011) and $490 per person (Borges et al., 2014). The reported mean annual antidiabetic costs in the two German studies had a two-fold difference; $520 per person (Jacob et al., 2017) and $1,080 per person (Ulrich et al., 2016), respectively.

It was observed that mean annual antidiabetic medicine cost was the significant component in the overall healthcare cost. The mean annual antidiabetic medicine cost varied between 8% per person (Singapore) to 72% per person (Argentina) (Elgart et al., 2014; Ng et al., 2015).

2.4.4 Discussion

This study compared to cost of antidiabetic medicines across economically developed countries as per definition by the World Bank (The World Bank, n.d.). Of note, it has been reported in the literature that 80% all the global health expenditure is estimated to be from the world's economically richest countries (Zhang et al., 2009). Even though, there were differences in the methodology across studies, the findings from this systematic literature review suggest that the mean annual direct cost makes up a significant percentage of the mean annual cost. In the Ng et al. study (Ng et al., 2015) which was conducted in Singapore, showed that the estimated expenditure related to direct cost was $1,580 per person/year. This number is significantly higher than estimates reported in India (Tharkar, Satyavani, & Viswanathan, 2009) and China (Wang et al., 2009). According to the authors (Ng et al., 2015), this difference is due to that the two other studies does not consider inflation in their cost calculations.

The high number of elderly patients in Northern Italy is reflected in the mean annual direct cost which is $7,600 per person (Demurtas et al., 2017)**.** The mean direct cost increases with the disease progression, the number of comorbidities and with the age of the patients. The relatively high mean annual direct cost is in line with the cost of diabetes type II in Europe (CODE-2 study) which found that the prevention of comorbidities would reduce the overall healthcare expenditures (Williams, Van Gaal, & Lucioni, 2002). This reinforced the importance of optimising the use of healthcare resource as well

as promoting prevention of diabetes and diabetic complications (Al-Maskari, El-Sadig, & Nagelkerke, 2010; Bahia et al., 2011; Borges et al., 2014; Lee, 2011; Ng et al., 2015).

The expenditures on mean annual medicine cost was reported to be low in a number of the reviewed countries. The mean annual medicine cost as percentage of direct cost was found to be 26% in Northern Italy (Demurtas et al., 2017), 30% in Spain (Mata-Cases et al., 2016a) and 29% in Germany (Ulrich et al., 2016). This is consistent with previous findings comparing expenditure on mean annual medicines across eight European countries (Jönsson, 2002). The lowest mean annual antidiabetic medicine cost per person was from Singapore (8%) (Ng et al., 2015). A number of factors can influence the mean annual medicines cost. The most common influences are use of generic medicines and reimbursement policies in the respective countries (Vogler et al., 2015).

It is interesting to note that although there was a general consensus that there has been an increase in the use of antidiabetic medicines since the early nineties it was only the study conducted by Jacob et al. (Jacob et al., 2017) which reported on prescription patterns along with the cost of medicines. The authors reported that the expenditure on mean annual medicines costs was lower for older drug classes such as metformin and sulfonylurea compared to newer drug classes such as DDP-4i, GLP-1RA and SGLT-2i. The reported differences can be explained by the availability of generic substitutes for the older drugs whereas some of the newer drugs still are under patent and hence are more expensive.

2.4.5 Limitations

This current review compared the *mean annual direct cost* and *mean annual antidiabetic medicine cost* reported in nine original studies across seven upper middle income and high income countries. A comparison of *mean annual medicine cost* according to drug classes was not possible as the reviewed papers did not report on how much was spent on each drug class individually.

The findings should be viewed keeping the differences in the included cost items in mind. This is a limitation which has previously been pointed out in the literature comparing the costs of medicines (American Diabetes Association, 2013; Bolin, Gip, Mörk, & Lindgren, 2009; Jönsson, 2002). It is also important to acknowledge that each country has its own healthcare system, and thus the cost of medicines plays different role. In the following paragraph some of the methodological differences in the papers are described: Firstly, the participants in the original studies were recruited from a variety of healthcare settings. One of the study which was conducted in multiple settings found that there was not any difference in findings in secondary and tertiary levels of care (Bahia et al., 2011). Borges et al. (Borges et al., 2014) reported that the study had only been conducted in one diabetes centre and might be a potential bias. Further, the study found that the *mean annual direct cost* may be underestimated as the Brazilian government had kept the prices of National Health Care cost frozen for years. Thus, the authors suspected their findings may not reflect the actual *mean annual medicine cost of T2D* in the country. The second notable difference between the studies is the definition of 'T2D'. To mention a few examples; The Elgart et al. study (Elgart et al., 2014), used the following definition when recruiting

participants; patients had a recorded ICD-10 code, aged between 20 and 75 years and a two-year follow-up at the hospital. In the Jacob et al. study (Jacob et al., 2017) the patients had a recorded ICD-10 code and they were aged over 40 years. A third example of a definition is in the study conducted by Ulrich and colleagues; if diabetes status was missing the self-reported diabetes status was used, in cases where onset of disease was after age 40 the diabetes status was assumed to be T2D and lastly in case of missing diabetes status data the patients was excluded from the study (Ulrich et al., 2016). Another study (Mata-Cases et al., 2016a) excluded patients who died during the observation period from the study. Despite differences in the clinical treatment of patients with T2D and type 1 diabetes, the use of ICD codes does not ensure that T2D patients treated with insulin diabetes are not wrongfully reclassified as type 1 diabetes.

Previous studies which did not distinguish between the cost associated with T2D and Type 1 diabetes showed mixed findings. One study conducted in the USA showed that it is not suitable to combine the two groups as type 1 diabetes is related to higher expenditure than T2D (Tao, Pietropaolo, Atkinson, Schatz, & Taylor, 2010). Another study conducted in Italy (Bruno et al., 2008) came to the similar conclusion. The study found that the cost of medicines in the two groups was 7.7 and 2.5 times, respectively. This was higher compared to the control group without diabetes (Bruno et al., 2008). On the contrary, other studies which did not differentiate between the patient group found their cost ratio to be somewhat similar in both groups (American Diabetes Association, 2013, 2018b).

2.4.6 Conclusion

The second systematic literature review sought to synthesize evidence on cost of antidiabetic medicines and compare the expenditure across economically developed countries. After adjusting for inflation, it was found that the expenditures on mean annual cost per person and mean annual medicines costs per person varied across the surveyed countries. The mean annual direct cost was found to range between $220 per person (Argentina) and $7,600 person (Northern Italy). The mean annual medicine cost was found to range between $140 per person (Singapore) and $2,990 person (Argentina). It was notable, that the reviewed papers did not use the same components in their cost estimates. Having a standardised use of terminology would had allowed for more realistic and directly comparable cost estimates.

2.5 Part IIII: Key summary points from chapter 1 and 2

The management of adults with T2D is mainly undertaken in primary care in England. Primary care clinicians see patients and use their clinical judgement to make prescribing decisions about suitable treatment for the patient. When prescribing for T2D the difficulty encountered by many clinicians is that the condition is complex, and additionally there are varying prescribing recommendations. Furthermore, while primary care clinicians are key to helping people with T2D managing their condition, they are also encouraged to involve the patients in the choice of therapy. This section aims to summarise findings from chapter 1 and 2 which informed the mixed-methods study design and development of the topic guide (study 1).

General practitioners' use of prescribing guidelines

- Previous UK-based studies which had investigated GPs' prescribing behaviors' showed GPs to be influenced by consult prescribing, hospital prescribing as well as patient behaviors.
- Existing studies on use of NICE guidelines in other therapeutic areas showed that complex and lengthy guidelines were often not followed by prescribers.

Diabetes care

- There are difference in regional preferences towards certain drug classes.
- High HbA1c level observed at first pharmacological treatment.
- Suboptimal dosing of metformin had been reported.
- Delay in treatment intensification was also commonly reported.
- Statistics from NDA showed that adults with T2D are routinely offered structured education in diet and lifestyle interventions. However, most patients do not attend these programs.

Prescribing trends in use antidiabetic drug classes

- Metformin has taken over sulfonylurea role as most commonly prescribed first-line treatment.
- DDP-4i is most commonly prescribed second-line treatment.
- There is reluctance around using thiazolidinediones.
- The use of SGLT-2i and GLP-1RA has gradually been increasing.

Treatment outcomes

- Statistics from NDA showed that adults with T2D in England have suboptimal treatment outcomes on currently prescribed therapies.
- The launch of new drug classes on the market was reflected in the choice of drug classes being prescribed in primary care.
- Reporting of adverse events and withdrawal of drug classes from the market had a negative impact on the use of drug classes.

- Clinical trials have shown an increased benefit of using newer antidiabetic treatments which have clinical benefits beyond their ability to reduce glucose levels.

Cost of antidiabetic medicines

- Treatment with older drug classes such as metformin and sulfonylurea are less expensive compared to treatment with newer drug classes such as DDP-4i, SGLT-2i and GLP-1RA.
- The increase in volume and cost of antidiabetic drugs was attributed to the launch and use of DDP-4i, GLP-1RA and SGLT2i. T
- Use of new therapies accounted for 41% of the medicines budget only divided over 9% of the total number of patients (Heald et al., 2018).

CHAPTER 3

Research design and applied methods

3.1 Research design

Chapter 3 presents the research philosophy and design used to address the research questions in the mixed-methods study. This thesis chapter begins with an introduction to the researcher's philosophical stance and use of theory in this research. Next, mixed-methods research strategies are described, and a justification of the approach taken in this research has been given. Then, the applied qualitative and quantitative methods are described in turn, and where relevant, alternative choices which were considered are discussed. This chapter is followed by chapter 4 and 5 which describe the specific research questions and findings of study 1 and study 2 of the mixed-methods study, respectively. Study 3 was a case study which had a different perspective than study 1 and 2 and hence the background for the study, methodology and methods as well as results have been described in chapter 6.

3.1.1 Preunderstandings and use of theory

In this section the researchers' philosophical stance and pre-understandings are described. This section is followed by a description of the applied conceptual framework which has been used for the qualitative research.

3.1.1.1 Preunderstandings

This study is concerned with primary care clinicians' antidiabetic medicines prescribing practices. Broadly, it was sought to explore the attitudes, knowledge and experiences which motivates the prescribing decisions among primary care clinicians. Much debate around mixed-methods research is related to which research paradigm should be superior (Ross, 2012). "*A paradigm is a basic set of beliefs that guide action*" (Guba, 1990, p. 17). The author of this PhD thesis has taken the stance that pragmatism is a partner for the mixed-methods research approach (Denscombe, 2008). The researcher is motivated by the belief that the current thesis would not be adequately answered by taking a qualitative or quantitative approach on its own (Johnson, Onwuegbuzie, & Turner, 2007; Tashakkori & Creswell, 2007). The PhD thesis is exploratory in nature and the research data was driven by ideas from the review of the literature (*chapter 1*) and from the conduct of systematic literature reviews (*chapter 2*). Qualitative interviews (study 1) which are typically associated with a constructivist paradigm were used to explore primary care general practitioners' (GPs) antidiabetic medicines prescribing practices. The follow-up studies, cross-sectional survey (study 2) and case study (study 3), adapted a positivist paradigm to expand on the findings from study 1. Creswell (2014) has described the key principles of the pragmatism paradigm as (Creswell, 2014, p. 11):

- Pragmatism is not committed to any specific system of philosophy and reality.
- The researcher is free to choose any methods and procedures which are suitable to answer the posed research questions.
- The researcher can use multiple methods of data collection and analysis within the mixed-methods study.
- Research always occurs in historical, social and political context.

Fitting with the pragmatism approach, qualitative (constructivist paradigm) and quantitative (positivist paradigm) research methods were chosen due to their suitability to answer the posed research questions. The rationale for a mixed-methods research design and justification for choosing an exploratory mixed-methods research design have been provided in sections 3.1.1.4 and 3.1.1.5.

3.1.1.2 Reflexivity

"*Reflexivity is the self-appraisal in research*" (Berger, 2015, p. 220). This refers to the researcher's own critical reflection of personal and philosophical beliefs about the research. The purpose of this section is not to remove any influence of the researcher on the research process but rather acknowledge its existence. Malterud (2001) states that "*preconceptions are not the same as bias, unless the researcher fails to mention them. If reflexivity is thoroughly maintained, personal issues can be valuable sources for relevant and specific research*" (Malterud, 2001, p. 484). Thus, it is pertinent to describe the preconceptions of the researcher, as these will impact how the researcher approaches the research. Berger (2015) has described three types of researcher positions as reflexivity: *1)* when the researcher is familiar with the subject area and shares the experiences of the study participants*, 2)* when the researcher moves from the position as an outsider to the insider position, *3)* when the researcher is unfamiliar with the subject area and experiences of the study participants. The author of this thesis is a community pharmacist (amongst other roles) and as such considers her role to be in between all three categories. My role as community pharmacist has made me familiar with the National Institute for health Care Excellence (NICE) prescribing guidelines and the sequence of using antidiabetic medicines. Being a pharmacist, the researcher had a good understanding of the indications, contraindications and side-effects of the involved antidiabetic medicines. However, the researcher was unfamiliar with the healthcare professionals' decision-making processes and the roles of the healthcare professionals within the diabetes teams. My understanding of the prescribing practices within primary care was limited. My assumption was that the poor management of patients with type 2 diabetes (T2D) was a result of poor self-management combined with the limitations of the healthcare systems.

3.1.1.3 Initial theory used in this research

The initial idea for this research was a conversation between the researchers' supervisors. It was observed that the use of metformin was suboptimal, and clinical inertia during treatment initiation was a challenge in diabetes care. As the researcher was introduced to a hypothesis which the supervisors had about the research topic it was only natural to review empirical evidence to test this hypothesis. When reviewing existing literature on the topic it was observed that behaviour change theories were used to predict or change clinicians' prescribing behaviours (Cameron, 2009). However, using a behaviour change theory was not found suitable for this research as prediction or change of clinical behaviours would require underlying understanding of the cause of these behaviours. Additionally, the essence of this research was not to develop a new theory but rather to explore what drives GPs' prescribing decisions and how it fits with what is already known about diabetes care. Alternatively, it was considered to not employ any theory at all. But although the researchers' understanding of the topic was limited the observations which were made during the research are not believed to be pure

due to the researchers background as a pharmacist (Cresswell, 2009). For this reason, it was decided to adapt theoretical orientation where developing a theory becomes the end point of the research (Cresswell, 2009). Punch et al. has described this use of theory as an inductive logic process which builds on observations from data to development of broad themes to a generalised theory (or broader explanation) (Punch, 2005).

As depicted in figure 3.1 the review of literature led to the understanding that there was a gap between clinical practice and current evidence on diabetes care.

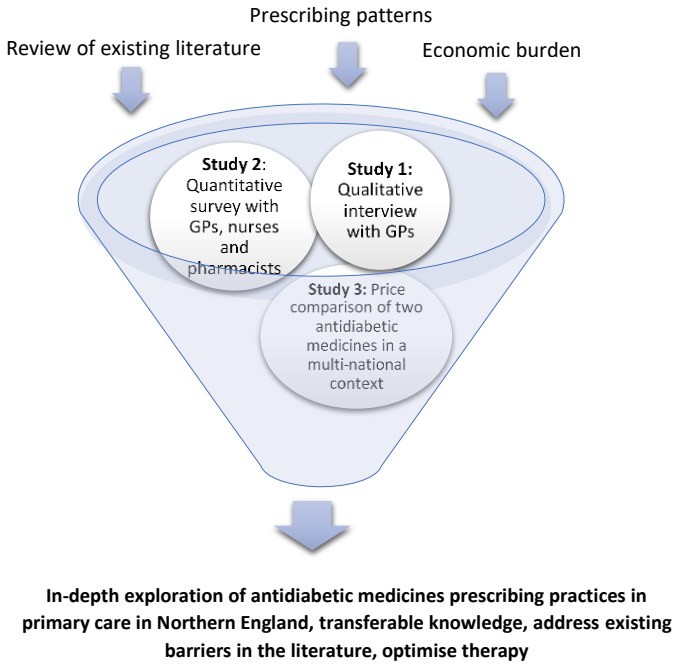


Figure 3.1 Exploratory mixed-methods study investigating antidiabetic medicines prescribing practices in primary care in Northern England.

The key lessons learned from the literature review (*as described in section 2.5*) informed the development of the topic guide which was used to collect the qualitative data. In the initial topic guide, the focus was on the GPs' antidiabetic medicines prescribing practices and the influences from NICE T2D guideline (NG28). However, during the pilot study it became clear to the researcher that Clinical Commissioning Groups (CCGs) are equally important drivers for decisions made by GPs. The development and piloting of the topic guide has been described in detail in section 3.2.1.2. Based on the theory/observations the researcher gathered data to generate themes and categories into patterns section 3.2.1.9. The findings from the qualitative data analysis are presented in chapter 4 and concludes with a conceptual model which describes the key influences in GPs antidiabetic medicines prescribing practices.

3.1.1.4 *Development and use of theory in this research*

Once the qualitative data analysis had been completed it became evident that the described influences on antidiabetic prescribing practices were embedded across multiple levels in the healthcare system. A sociological framework was adapted to provide a deeper interpretation of the collected data. The conceptual framework used was originally developed by Dahlgren and Whitehead (Dahlgren & Whitehead, 1991) and used in various population health settings (CCSDH, 2015). The healthcare system in England consists of multiple organisations who work together to provide the best possible care to patients (Department of Health, 2013). Figure 3.5 (left circle) is an illustration of the healthcare system which has been divided into three levels.

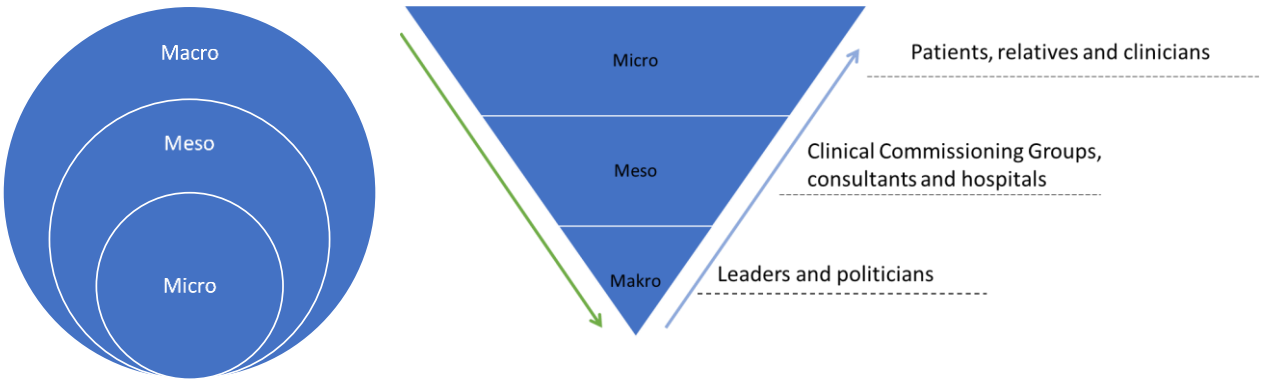


Figure 3.2 Interlink between micro, meso and macro levels in the healthcare system.

In this mixed-methods study the micro, meso and macro levels in England can be described as:

- *Micro levels*: refers to the individual clinicians and the decisions made during day-to-day consultations with the patient.
- *Meso levels*: refers to Clinical Commissioning Groups (commissioner and provider organisations).
- *Macro levels*: refers to national prescribing policy decisions influenced by research evidence (guidelines) and clinical governance mechanisms (NICE).

Addressing the problems in the healthcare system with a multilevel theory approach (depicted in figure 3.2, circle) can offer an integrated way to bridge the complexity between current day-to-day prescribing practices (micro level), CCGs (meso level) and NICE guidance (macro level). Although the multilevel model depicts three distinct levels of healthcare in real-world settings they are often found to be overlapping and linked via feedback loops (CCSDH, 2015). When each of the levels work effectively and complement each other, the healthcare system is able to deliver better health and in an ideal world also improved health outcomes (WHO, 2002). However, in the management of chronic conditions the flow between the three levels of healthcare is often found to be suboptimal (WHO, 2002). This is for instance seen with lack of distinction between the roles and responsibilities across micro, meso and macro levels (CCSDH, 2015).

Issues at one level of the healthcare system are often linked with other levels through the feedback loops. If primary care clinicians for example are not able to provide care due to lack of training this is a micro level issue as it is related to the delivery of care to the patient. As the healthcare organisation is responsible for providing appropriate training and access to antidiabetic medicines this could also be considered a meso problem. Further, it is the responsibility of the policy makers to ensure that the healthcare needs of the population are met through appropriate regulations and guidance hence it could also be a macro level issue. However, if the hierarchy is turned bottom-up (figure 3.2, triangle) the primary care clinicians could make demands towards having increased influence on the distribution of resources and power to influence the regulations and clinical guidelines through involvement on meso and macro levels (*discussed further in section 7.3.3*).

3.1.1.5 Strengths and limitations of the conceptual framework

This research resulted in the development of a conceptual model which connected the findings from study 1 with existing literature. The conceptual framework cannot be used to develop a theory but is useful for policy and decision makers to identify areas which needs optimising across the healthcare system. As mentioned above the three levels are not distinct and issues on one level in the healthcare system feeds back via loops to other levels. In order to improve treatment outcomes, it is necessary to address patient and healthcare professional related barriers to clinical inertia around treatment intensification (micro level) and the challenges with translating meso and macro level guidance into clinical practice.

3.1.2 Mixed-methods methodology

This section briefly describes mixed-methods research strategies. It then provides a rationale for choosing a mixed-methods study and justifies the use of exploratory mixed-methods research.

During the familiarisation with mixed-methods research a mixed-methods research book chapter was published by the author of this thesis (Ramzan, Hadi, & Babar, 2019a). The book chapter describes the foundations of a good mixed-methods study, typologies of mixed-methods, how to integrate findings, challenges when undertaking a mixed-methods study and also how to evaluate the quality of mixed-methods studies. This book chapter has been used as inspiration when this current methodology has been written and has been cited as appropriate.

3.1.2.1 Mixed-methods research strategies

Tashakkori and Teddlie (2003) identified around forty types of mixed-methods research strategies in the literature (Tashakkori & Teddlie, 2003). However, the purpose and use of many of these strategies were not always clear to researchers (Cresswell, 2009). The four most commonly used typologies of mixed-methods research are convergent parallel design, embedded design, explanatory sequential design and exploratory sequential design. The research designs as proposed by Creswell et al. (Creswell & Plano Clark, 2011) are briefly described below*:*

The *convergent parallel design* is used when the qualitative and quantitative component is carried out independently but concurrently i.e. the data of each component is collected, analysed and the findings are integrated during the interpretation stage. Both components are given the same priority. The method is also referred to as 'convergent parallel design', 'current triangulation', 'simultaneous triangulation' and 'parallel study design' (Morse, 1991; Teddlie & Tashakkori, 2009). The convergent parallel design is useful to gain a complete understanding of the posed research questions as it collects 'different but complementary data' (Creswell & Plano Clark, 2011). The strength of the method is that it overcomes limitations of one method and can be used to confirm and validate findings through triangulation of findings from the two components.

In the *embedded design* one component acts as a principal method and the other component adapts a supportive role (Greene, Caracelli, & Graham, 1989). Priority is given to the principal component in the research design. Depending on the posed research questions, the data can either be collected concurrently or sequentially. The embedded research design is suitable when all posed research questions cannot be answered by a single component study (Morse, 1991; Teddlie & Tashakkori, 2009).

The *explanatory sequential design* employs the use of data collection in two clearly distinct stages. In the explanatory sequential design, the quantitative data is collected, analysed and interpreted first, and given priority to answer the posed research questions. In the next stage qualitative data is collected with the intent to explain findings from the quantitative component.

The *exploratory sequential design* also employs the use of data collection in two clearly distinct stages. In this research design the qualitative component is given priority to answer the research questions. Following this, the quantitative data are collected based on findings from the qualitative component. In this research design the qualitative results are used to develop or inform the quantitative study (Greene et al., 1989). In this mixed-methods study an exploratory mixed-method strategy has been used. The rationale and justifications for the chosen research design are given in the next sections.

3.1.2.2 Rationale for choosing mixed-methods research design

Mixed-methods research is often described as a flexible approach. However, this increases the importance of researchers sufficiently planning the research design and justifying their choice of conducting a mixed-methods study (Creswell, 2007). The choice of mixed-methods research strategy should be driven by the posed research questions and should not depend on personal preferences towards qualitative or quantitative research methodologies (Creswell, 2007). For this reason, it is important to reflect on "*how, when and why different research methods might be combined*" (Bryman, 1988, as cited by Bryman, 2006, p. 99). Bryman (2006) analysed ways qualitative and quantitative components are combined in practice and based on this analysis sixteen reasons (triangulation, offset, completeness, process, different research questions, unexpected results, instrument development, sampling, credibility, context, illustration, utility, confirm and discover, diversity of views, enhancement, other/unclear and not stated as reasons) for conducting mixed-methods research studies were reported

(Bryman, 2006). Additionally in 1989, Greene et al. (1989) identified five reasons for conducting a mixed-methods study (Greene et al., 1989):

- *Triangulation* – refers to using more than one method while studying a research question in order to increase the credibility of results.
- *Complementarity* – achieve a better understanding of the posed research questions and/or clarify the findings.
- *Development* – the use of multiple methods in synergy, where one method is used to inform the other method.
- *Initiation* - where the findings from one study raises questions and/or contraindications which require further clarification through a follow-up study.
- *Expansion* – the use of two synergic methods widens the breadth and range of inquiry.

In this PhD research, the five basic reasons for conducting a mixed-methods study design as identified by Greene (1989) were fulfilled. Current study placed emphasis on *complementarity*, *development* and *initiation* as the literature search led to a number of questions which called for exploration. On completion of the qualitative research, it was clear that some issues needed further clarification through a second study. The findings from the qualitative were therefore used to inform the survey instrument in the quantitative study.

The advantage of using mixed-methods research design for this thesis is that it offers a broader understanding of the research area by combining the strengths of qualitative and quantitative methods. The researcher's motivation for choosing mixed-methods research design lies in the nature of the posed research questions and other researchers' experiences with conducting similar health services research studies. The review of literature (chapter 1) showed that unclear guidance can lead variable responses among healthcare professionals (Bateman, Good, Afshari, & Kelly, 2003; Hawton et al., 2009). The current NICE guidance suggests prescribing medicines with the lowest acquisition cost within each drug class (NICE, 2015) which means that the CCGs can more freely provide local guidance based on their understanding of the available evidence on antidiabetic medicines (NHS, n.d.-a). Existing research on prescribing behaviours in England mostly had a quantitative focus and had researched prescribing trends and cost of antidiabetic medicines (Curtis et al., 2018; Dennis et al., 2019; Wilkinson et al., 2018). These studies were not able to explain the reasons for variation in choice of treatment after metformin. Expenditure on antidiabetic medicines was associated with choice of drug as older treatments were found to be less expensive than newer treatments (Curtis et al., 2018; Heald et al., 2018). While retrospective studies are useful to identify variables associated with prescribing choices, they do not explain underlying reasons for prescribing behaviours. In these circumstances a qualitative approach is useful to further the understanding of observed prescribing practices. Previous studies describing factors influencing GPs' prescribing decisions used qualitative and quantitative methods (Bradley, 1992a, 1992b; Carthy et al., 2000; Jacoby et al., 2003; Prosser et al., 2003; Prosser & Walley, 2003, 2005).

None of the existing survey tools could be adapted in the current research as they were not based on the NICE T2D prescribing guideline but were used as inspiration during the development of the qualitative and quantitative research tools. Moreover, previous studies identified lack of triangulation of quantitative and qualitative components as weakness of the research design. In the study conducted by Buusman et al. the importance of using qualitative and quantitative research approaches to produce a holistic understanding of the topic (Buusman, Andersen, Merrild, & Elverdam, 2007). The authors stressed that that using a combination of the two methods could produce robust data which could triangulated and there thereby validate the collected data. In context of the current research getting a holistic understanding of what influences primary care GPs views on antidiabetic medicines is important for the development of prescribing guidelines and medicine optimisation strategies which promotes clinically appropriate and cost-effective prescribing in primary care.

3.1.2.3 Justification for choosing exploratory research design

As the researcher did not have preferences towards any mixed methods strategy, familiarisation with typologies within mixed-methods research led to the decision of answering the posed research questions through an exploratory research design. This choice was guided by Creswell and Clark's four questions related to design characteristics which can help the researcher to choose an appropriate mixed methods strategy. As described by Creswell et al. (Creswell & Plano Clark, 2011) and adapted from (Ramzan et al., 2019a):

- First, the researcher should decide the ***level of interaction*** between qualitative and quantitative strands. Will the qualitative and quantitative strands be kept independent or interactive?
- Secondly, the researcher must decide on the ***timing of data collection*** of both qualitative and quantitative strands. Qualitative and quantitative data can be collected sequentially or concurrently.
- Thirdly, the researcher needs to consider weighing of each component in mixed-methods design. Will the quantitative or qualitative component be given ***priority*** in answering the research question, or will they be weighed equally?
- Lastly, the researcher must decide the ***timing of integration*** of two datasets as this can happen at different phases of the research (i.e. during data collection, data interpretation etc.).

After careful consideration of strengths and limitations of each mixed-methods research design the exploratory sequential design was chosen. This study design is particularly useful to assist in developing research instruments and in the literature it has also been referred to as "the instrument development design" (Creswell, Fetters, & Ivankova, 2004) and "quantitative follow-up approach" by Morgan (1998) as cited in (Creswell & Plano Clark, 2011). As mentioned earlier, in exploratory designs the qualitative component is given priority and carried out before the quantitative component. Since there was a limited literature in context of T2D prescribing practices in England it was considered appropriate for the current mixed-methods study to start with an explorative investigation. Study 1 sought to understand how GPs make prescribing choices and when and why they would use NICE guidance during their daily practice.

This study identified a number of factors which influenced GPs prescribing choices such as personal attributes and choices, characteristics of drug classes, local prescribing policies, external influences such as local consultants and hospital prescribing. Due to the nature of interviews, it was not possible to identify patterns on what the GPs' preferred drug classes at each stage of treatment were, who they would seek guidance from regarding appropriate choice of treatment when they are in doubt of the next step of treatment, and for which clinical representation of the patients they would be seeking guidance from another healthcare professional. In the follow-up study (study 2) key findings from the first study were explored. Getting a better understanding of primary care clinicians self-reported prescribing preferences was of particular interest as these patterns combined with qualitative interviews may further the understanding of how the gap between differences in prescribing choices across England could be narrowed. A flow diagram of the described mixed-methods research phases has been presented in figure 3.3.

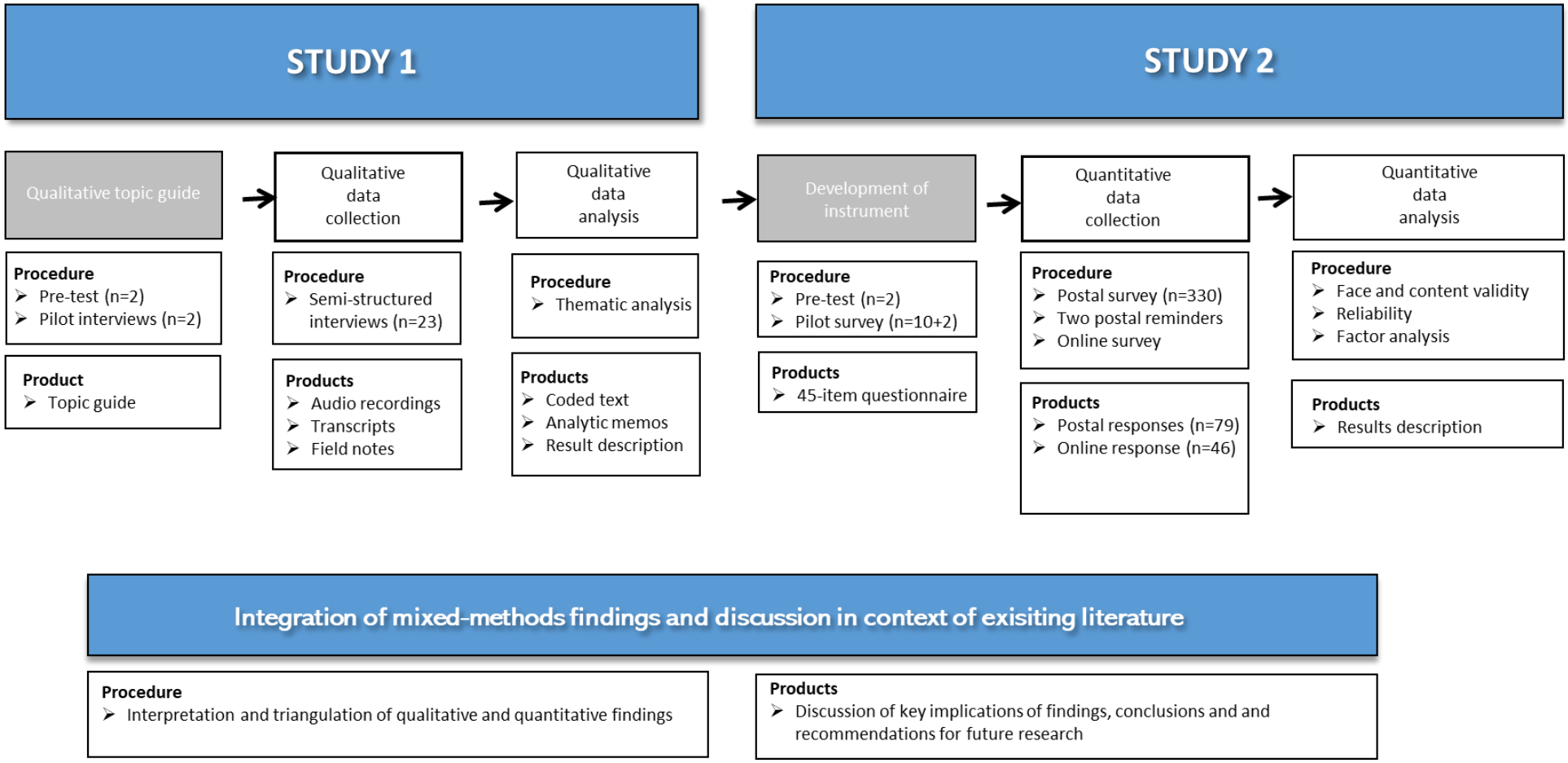


Figure 3.3 Flow diagram of procedures and integration of study 1 and study 2 of the mixed-methods study.

3.1.3 Qualitative research methodology

As depicted in figure 3.3, study 1 was conducted using qualitative methods. A wide range of qualitative research methods exist, and this may also be the reason researchers across disciplines do not agree on a single definition of qualitative research (Holloway, 2005). The qualitative research paradigm takes a constructivism stance. It is often described as non-positivist and the pragmatic assumptions are that there is more than one correct version of reality and knowledge (Braun & Clarke, 2013; Creswell, 2014). Qualitative research methods are concerned with making sense of the *what, when, where* and *who* of a certain phenomenon. This is achieved by collecting words as data to understand and explain the described experiences of people (Braun & Clarke, 2013; Holloway, 2005). After much resistance and controversy about the usefulness of qualitative methods they are now commonly used in healthcare research (Austin, 2019). The qualitative methods makes use of textual or narrative data (e.g. interview transcripts, diaries, field notes, photographs and videos) as opposes to quantitative methods which makes use of numerical data (Avis, 2005). When using qualitative methods, the researcher seeks to see the world through the lens of the participant (Creswell, 2007) and learns about their experiences through engagement and report (Spradley, 1979). Avis (2005) further elaborates "*methodological naturalism holds that research techniques should be familiar to people being studied, respect their beliefs, have similarities with normal social interaction, and leave people undisturbed as far as is possible*" (Avis, 2005). Lastly, it is important to mention *self-reflexivity*. As the researcher is a tool in the data collection process, it is important to reflect and be aware of one's pre-understanding and share meanings with the participants (described above in section 3.1.1.1).

Qualitative research was selected for this study as it is characterised to generate in-depth understanding of the participants' experiences, knowledge, feeling, attitudes and motivation (Kaae & Traulsen, 2015). This study sought to understand how GPs make antidiabetic medicines prescribing choices including how NICE prescribing recommendations influence their prescribing choices. The purpose of qualitative interviews was to gather descriptions of the real-world of the interviewees (Kvale, 1983) and record the recognised and unrecognised differences in the experiences of the GPs. According to Braun and Clarke "*interviews are ideally suited to experience-type research questions*" (Braun & Clarke, 2013, p. 81). Face-to-face interviews were ideal for this study as the focus was to explore *how* and *why* the GPs prescribe as they do rather than if these prescribing practices are in accordance with NICE prescribing guidelines. Semi-structured interviews were chosen for this qualitative study as the topic guide provides a flexible framework for the conversation with interviewee but at the same time it is flexible enough to let the interviewer decide the nature and depth of the information which is shared during the interview (Judith Green & Thorogood, 2009).

Alternatives such as telephone or internet interviews may have increased the availability and access to the participants. However, these tends to be shorter than face-to-face interviews, using visual aid to assist during the interviews would have been challenging (i.e. . GPs showing their prescribing software, guidelines and course materials) moreover behaviour and body language could not have been observed during the interview (O'Cathain, Murphy, & Nicholl, 2008). Observations were not found suitable for this study as the working environment of the GPs may be difficult to observe. Additionally, this would also

be logistically challenging as all patients seen by the GP do not have T2D and it would require consent from the employing organisation to sit in during consultations.

Traditionally, quality of research has relied on standards of quality and evaluation such as checklists, which if used as intended, would indicate rigour within the research process (Creswell & Plano Clark, 2018). The choice of checklists was based on what had been previously seen used by other health services researchers in medical and health journals (Tong, Sainsbury, & Craig, 2007). In study 1, the 32-item consolidated criteria for reporting qualitative studies (COREQ) was adapted for describing the research team, methods, context, findings, analysis and interpretations (Tong et al., 2007) and presented as appendix 4. While the existence of checklists was appreciated the use of these does not ensure the quality of the research (Amin et al., 2020) and nor do they go into the rationale for selecting and undertaking strategies for ensuring rigour (Hadi & Closs, 2016). Quality considerations of the qualitative study are described in section 3.2.1.10.

3.1.4 Quantitative research methodology

As depicted in figure 3.3, study 1 was followed by study 2 using quantitative methods. Green et al. describe quantitative research as "*research in which things are counted*" (Green, Norris, Pauline. , 2015, p. 31). The referring to *things* could be people, medicines, opinions or behaviours. Quantitative research plays an important role in healthcare research because it allows generalisation of findings (Green, Norris, Pauline. , 2015). Quantitative research methods have an objective understanding of the reality and is usually associated with a positivist worldview (Seers & Critelton, 2001). It is often described as being reductionistic and deductive. Data collection is described as systematic and rigorous (Gerrish, Lacey, & Cormack, 2010) and the findings are expected to be replicable and generalisable (Parahoo, 2014). Surveys seek to describe *what* things are like rather than *why* they are in a particular way (De Vaus, 2014) and hence complements findings from qualitative studies well. They are often used to measure the health needs of a population and are a particularly useful tool to inform the planning and allocation of health resources (De Vaus, 2014).

This mixed-methods study used the observational study approach. Surveys are non-experimental studies which are designed to collect specific information from individuals of interest and are used in this current study. A questionnaire survey is defined as cross-sectional when the collection is done over one pre-defined time period (Bryman, 2012). Data can be delivered as self-administration questionnaires through hand delivery, post or as online surveys. Other data collection approaches include face-to-face interviews and telephone interviews (Parahoo, 2014). These two methods are mostly associated with qualitative research methods. An online survey was considered, but due to the low response rate from online surveys (Fan & Yan, 2010) this was kept as a secondary option (described further in section 3.2.2.5).

In study 2, a checklist for the things to consider when selecting, designing and developing a questionnaire was adapted for the quantitative study (Boynton & Greenhalgh, 2004). The researcher critically used the checklists to guide the conduct of the research and the description provided in this thesis. Checklists items has not been 'forced' to fit into the research (Cheek, 2015) and hence a number

some items in the checklist are marked not applicable (appendix 5). Quality considerations of the quantitative study are described in section 3.2.2.11.

3.2 Description of applied methods

This section presents the applied methods in study 1 study and study 2 in turn.

3.2.1 Qualitative component: Semi-structured Interviews

In the following sections the qualitative methods will be described by a detailed encounter of the planning, development of research materials, analysis and reporting of the qualitative study (study 1). Where applicable alternative approaches considered will also be described.

3.2.1.1 Ethical approval

The mixed-methods study was granted ethics approval from the School Research Integrity and Ethics Committee (SRIEC) at University of Huddersfield on 16th November 2018 (reference: SAS-SRIEC-1611-18-1). The approval has been attached as *appendix 6, ethical approval 1*.

An online ethics application was submitted through the Integrated Research Application System (IRAS). The University of Huddersfield acted as sponsor for the study and as described above the university had granted ethical approval prior to applying for IRAS approval. The online application required submission of an online application and supporting documents including research protocol, flyer for social media (appendix 7), letter of invitation (appendix 8), participant information sheet (appendix 9), final interview guide (appendix 10), informed consent form (appendix 11), SRIEC ethical approval (appendix 6), public indemnity document, decision from the Research Ethics Committee (appendix 12). The IRAS application was handled by an assessor from the Health Research Authority (HRA). The HRA assessor discussed the research with this researcher and advised that the project did not require HRA approval. A written email confirmation was received from the assessor who based the decision on fact that the study involved NHS employees as participants solely by virtue of their professional capacity rather than in relation to their employment by a specific NHS organisation (*appendix 13, HRA approval not required*). For this reason, the application with IRAS was withdrawn.

The project was planned in compliance with the University of Huddersfield's Research Ethics Policy and General Data Protection Regulation (GDPR) 2018. For this reason, the participants were ensured confidentiality and data protection; serial numbers were given to all participants and documents containing contact names/details were kept electronically on a password-protected University server. The participants were also informed about their right to withdraw from the study at any stage without giving any reason. Further, informed consent was obtained from the participants; they were given necessary information about the project, opportunity to ask questions and following these steps written consent for participation was taken (appendix 11).

3.2.1.2 Topic guide

A key component of successful use of interviews is good preparation. Developing and piloting an interview guide enables the researcher to interact with the participant and build rapport (Braun & Clarke, 2013). Spending time on refining and improving the interview guide is important as it allows the researcher to think about difficulties that might be encountered (questions, wording of sensitive topics) and also allows the researcher to reflect on how these difficulties will be handled in the interview situation (Smith, 1995). It is important to emphasise that an interview guide is not *fixed* and can evolve during the data collection process as new issues arise (Braun & Clarke, 2013).

The interview guide was informed by recommendations in NG28, review of the literature (chapter 1) and systematic literature reviews(chapter 2). The Venn diagram presented in chapter 1 (figure 1.2) was used to mind map areas which were relevant to antidiabetic medicines prescribing practices, and a list of questions was produced based on this. The draft interview guide was presented to the supervisory team. The aim of these discussions was to identify potential drawbacks in the draft interview guide. Then, the content of the revised draft interview guide was discussed with two diabetes experts and adjusted according to their recommendations. The diabetes experts were involved in the PhD research due to their interest in the research topic and involvement in the diabetes community in the North of England which enabled them to give recommendations and insight based on their experience in the field. They for instance suggested to add a question about which guidelines the GPs were aware of besides NG28. Further, recommendations were given in terms of wording of questions e.g. instead of "*can you mention an example of a medicine you would prescribe during treatment initiation?*" it would be better to ask "*what medication do you usually commence a newly diagnosed patient with*?". The redrafted interview guide was reviewed several times by the researcher and following a last discussion with the supervisory team the interview guide was deemed ready for piloting.

The researcher trialled interviewing skills and techniques with one practice pharmacist and one PhD researcher. The mock interviews gave the researcher opportunity to test the recording equipment, track time and ensure clarity of the posed questions. Following the mock interviews, the interview guide was pilot tested on two GPs from the survey area. During the pilot interviews it was observed that GPs also described the influence of CCGs on their prescribing practices, and this was added as a question under section C in the interview guide. Further adjustments were made in terms of wording and order of questions. The final version of the interview guide was used during the remaining interviews (*Appendix 10*). Table 3.1 describes the themes and questions covered in the final version of the interview guide. It is important to keep in mind that an interview guide serves as a flexible tool to direct the conversation between the interviewer and respondent (Lindlof & Taylor, 2002), and for this reason the outlined structure was not followed rigidly during the interviews.

Table 3.1 Themes and questions covered in the final interview guide.

Introduction and preliminary activities
Self-introduction to respondent
Reminder about project background aims and objectives
Seek permission to audio-record interview
Reassure confidentiality (responsible management and storage of data during transcription, analysis and reporting)
Information about right to withdrawal
Take consent for participation
Section A – *Demographics*
Background information about respondent
Information about general practice
Section B - *GPs perception on management of adults with type 2 diabetes in the England*
Describe their experience with using NG28
Describe their experience with using other type 2 diabetes treatment guidelines
Describe step-wise approach treating type 2 diabetes patients
Views on drugs they would like to see recommended by NICE
Section C – *Views and perception regarding the role of NICE in management of adults with type 2 diabetes*
Views on the role of NICE in the healthcare system in England
Describe how NICE influences prescribing decisions
Describe the communication between NICE and GPs
Describe how they voice concerns with the prescribing guideline to NICE
Describe their knowledge about the members in the NICE committees
Describe their views on the decision-making process undertaken by NICE
Section D – *Views and perceptions regarding the role of GPs when prescribing medicines for management of adults with type 2 diabetes in England*
Describe the role of the GP in the treatment of patients with type 2 diabetes
Describe the role shared decision-making play for achieving desired treatment outcomes
Describe the role of NICE for achieving desired treatment outcomes
Describe how NICE influences prescribing decisions*****
Describe how the local CCG influences prescribing decisions
Describe how the practice management influence prescribing
Section E – *Views and perception regarding the cost of medicines*
Describe how the price of medicines influence prescribing decisions
Describe how you stay informed about the price of medicines
*Question repeated from section C

3.2.1.3 Research sites

The research sites were defined as CCGs in North East and North West & Yorkshire as per definition of NHS England in July 2018. A complete list of CCGs in the survey areas has been attached as appendix 14 and includes 66 CCGs covering 2,342 general practices. It was learnt from the literature that there is a geographical variation in the prescribing of antidiabetic medicines across England (Curtis et al., 2018; Dennis et al., 2019; Wilkinson et al., 2018) and as it was the aim of this research to get a breadth of GPs' prescribing practices it was decided to focus on the Northern area. During the discussion with diabetes experts alternatives such as case studies in one or two CCGs was explored. However, the diabetes experts advised that there is an enormous difference between the populations living in for instance Manchester and Cumbria (e.g. younger population in Manchester and older

population in Cumbria) and hence focusing on specific areas would not create results which would reflect prescribing practices across England.

3.2.1.4 Sample

As mentioned earlier, the exploratory research design was chosen for this study. Initially It was intended to interview a range of primary care clinicians (GPs, nurses and practice pharmacists) about their antidiabetic medicines prescribing practices. However, after reviewing the literature it became evident that the GPs maintained the oversight of treating patients with T2D and it was decided to focus the qualitative study on the prescribing practices and views of GPs. The participants were screened against the following inclusion and exclusion criteria:

Inclusion criteria:

- Currently registered as GP with the General Medical Council.
- Currently GP registrar and working in primary care.
- General practice based in any CCG in the North of England.
- Any level of experience with treating patients with T2D.
- Willing to participate.

Exclusion criteria:

- Retired or stopped working in primary care.
- GPs practicing in CCGs outside the North of England.

The participants were recruited for the study between 1 January 2019 to 31 May 2019. The participants were approached through social media (Facebook, LinkedIn and Twitter) and within the researcher's personal network. Initially a flyer (*Appendix 7)* with brief information about the study concept, target audience and how to get involved in the research was circulated. When prospective participants contacted the researcher through e-mail, private messages on social media or text messages they were screened against the eligibility criteria. All eligible prospective participants who showed interest in participating in the study were sent the letter of invitation (*Appendix 8*) with further information about the study and an open invitation to let the researcher know about their availability to conduct the interview. The name of the participant was replaced by a serial number. This information along with e-mail address, confirmed date, time and place of the interview were saved in a password-protected Microsoft Word (version 2008) document.

3.2.1.5 Sample size

There is a certain degree of controversy regarding the appropriate sample size when conducting qualitative research. The purpose of qualitative research is not to recruit a statistically representative sample of participants (Pope, Ziebland, & Mays, 2000). Crouch et al. pointed out that a qualitative study is small and aims to gather an in-depth understanding of the investigated phenomena rather than trying

to collect generalisable findings (Crouch & McKenzie, 2010). It is commonly seen in health services research that the sample size is relatively small and often includes between 5 to 50 participants (Creswell, 2007; Ritchie, 2003). Other researchers propose a minimum of six participants to understand the essence of an experience (Morse, 2000). Green (2009) suggests that saturation of an interview based study often occurs after approximately 20 interviews (Judith Green & Thorogood, 2009). As the recommendations in literature varies it is important that the researcher takes a stance a has a clear strategy for when they will stop conducting interviews. In this study the sample size was guided by data saturation and information redundancy. Immediately after completing each interview the researcher made handwritten notes on key points, new information which was generated from the interviews and anything which the researcher's attention was drawn by (thoughts, feelings and reflections) in order to use them during data analysis. The researcher continued to interview participants until no new information was generated from the interviews. After conducting 18 interviews the author did not generate anymore new themes from the interviews. Three additional interviews were conducted to ensure data saturation, resulting in a total of 21 interviews.

3.2.1.6 Recruitment

Braun and Clarke (2013) emphasises that "*qualitative research is not a single thing, although people who don't understand it often treat it as if it were*" (Braun & Clarke, 2013, p. 20). On the contrary, qualitative research is a rich diverse and complex field (Madill & Gough, 2008). The participants sample must be selected carefully as it affects the quality of the qualitative research (Coyne, 1997). In the qualitative research methods the sample is not expected to be representative of the study population (Austin, 2019) because qualitative studies explore knowledge, beliefs and attitude which are not normally distributed within a population (Marshall, 1996). Through interviews, patterns of perceptions, attitudes and thoughts on a given subject area can be explored. Qualitative research allows the researcher to identify similarities and differences in the participants' accounts of the reality. It should be noted that the interviews are an account of the participants' own perception of the reality and hence not necessary the true description of events (Kaae & Traulsen, 2015).

The participants for this part of the study were recruited through convenience sampling. This is also called 'accidental sampling' and is often used in health services research to overcome logistic issues (Austin, 2019). This means that participants were recruited to the study without using a structured approach to recruitment. The sampling strategy was suitable for this study as the literature review identified geographical location and experience with prescribing as factors which influences GPs prescribing choices and hence it was the aim to include participants across the research site. The GPs were encouraged to participate in the study regardless of their level of experience with prescribing for patients with T2D (see section 4.3.3.2 for inclusion criteria). It was noticed that most of the prospective participants who showed interest in the study had varying experiences with prescribing antidiabetic medicines. Less experienced antidiabetic medicines prescribers often wanted confirmation that they were eligible to participate in the study due to their limited experiences. Morse et al. (Morse, 1991) emphasised that sampling must be appropriate and defined a "good" informant as *one who is articulate reflective, and willing to share with the interviewe*r' (Morse, 1991). Keeping this in mind, all GPs who

met the inclusion criteria were invited to participate in the study. Only two participants who had shown initial interest in the study dropped out without further explanation.

3.2.1.7 Interview setting and data collection

The interviews were conducted by the author of this thesis. On the day of the interviews, the researcher went to the GPs preferred meeting place. The interview place was decided by the participants as the interview setting influences the nature and quality of the data generated (Green & Hart, 1999). Most participants preferred the interview to be conducted in their office in their general practice.However three interviews were conducted in the participants' homes and one interview was conducted in a café. To ensure the privacy of the participant as well as safety of researcher and participant all interviews took place in a quiet place where nobody else could listen to the conversation. Further, the interview was paused if family members of the participants had to walk through the room where the interview was conducted.

As outlined in table 3.1 the researcher would start with an informal introduction of herself and her interest in the project followed by a reminder of the aim and objectives of the research. The participants were made aware that they could stop the interview at any point without having to explain anything. It was anticipated that the interview would last between 40 minutes and 60 minutes. Most of the interviews were completed within this time frame. Once this was explained the participants were asked to sign the consent form (appendix 11). Permission was also obtained to audio-record the interview and use quotes from the interview in the dissemination of findings.The GPs were also asked if they would be interested in providing feedback on key findings from the qualitative data analysis (explained further in section 3.2.2.6).

3.2.1.8 Data management

After completion of the interviews the GPs were provided a £100 Amazon voucher. This was deemed a reasonable reimbursement for their time and in accordance with common practice in health service research**.** The participants were asked to sign receipt of gift card acknowledgement (appendix 15). A copy of the gift card acknowledgement receipt was given to the postgraduate office at the University of Huddersfield for logistic purposes. The original copies of the consent form and gift card acknowledgement receipt were kept under lock and key. The data from the audio recorder was transferred to a password protected university server and deleted from the recording device. All interviews were transcribed by the researcher and checked for accuracy. Once the transcriptions were completed a second researcher listened to the audio recordings to make a final check for accuracy.

3.2.1.9 Data analysis

In the literature it has been described that the process of data analysis is often not described in great detail in qualitative research studies (Lau & Traulsen, 2017). Further, there is not much literature on consensus on how to perform as well as maintain rigour in thematic analysis (Braun & Clarke, 2006). A number of qualitative data analysis methods are available in the literature. It is the researchers' responsibility to choose a method which is appropriate to answer the research objectives (Smith & Firth,

2011). Bryman (2012) argues that thematic analysis is not a method in its own right but a tool used in other methods (Bryman, 2012). Braun and Clarke (2006) argue that it can in fact be considered a research method (Braun & Clarke, 2006). A grounded theory approach was also considered for the analysis of the qualitative data. Previous literature had portrayed a complex picture of prescribing practices in primary care which were influenced by multiple influences on prescribing choices and hence the researcher had doubts whether a central theory could be developed. As described in section 3.1.1.1.2 although the researcher kept an open mind towards development of a theory, the researcher was aware that this research was more likely to produce a rich description of antidiabetic medicine prescribing practices in primary care and offer a deeper understanding of how influences on prescribing choices links with the evidence to practice gap and perhaps help refine or develop existing theories. Strauss and Corbin recognise that not all projects are suitable for selective coding theory development and may instead aim to conduct a thematic analysis and conceptual development (Corbin & Strauss, 2015).

It was decided to conduct a thematic analysis on the qualitative. Thematic analysis has been described to be a useful method to examine the views of participants and highlight similarities and differences in their world views (Braun & Clarke, 2006). The approach to thematic analysis as described by Braun and Clarke is flexible and easy to adapt in different research approaches. For this reason, the authors stresses the importance of describing the epistemological context in which it is used. The reason for choosing thematic analysis as described by Braun and Clarke is due to its flexibility and adaptability. As this essentially is an exploratory study it was important to use an analysis technique which allowed the findings to differ from the initially stated research objectives. The data was coded and thematised with the intention to provide a descriptive level of data analysis (what is being talked about) and at the same time provide an interpretation (how and why are they talking about it) of the data. As described above a grounded theory approach would not have allowed the same flexibility.

In order to give the process of data analysis structure and ensure transparency in reporting of how the data was analysed, Braun and Clarke's six step method was adapted (Braun & Clarke, 2006). However, it should be noted that the six steps are not required to be carried out in a sequential order. The data analysis is described as an iterative process where the researcher can go back and forth between the six steps (figure 3.4). Braun and Clarke emphasise that the key to successful thematic analysis is not in following the steps in a linear fashion but rather in the researcher's own abilities to analyse the data. In the following section the researcher has described the applied approach to thematic analysis.

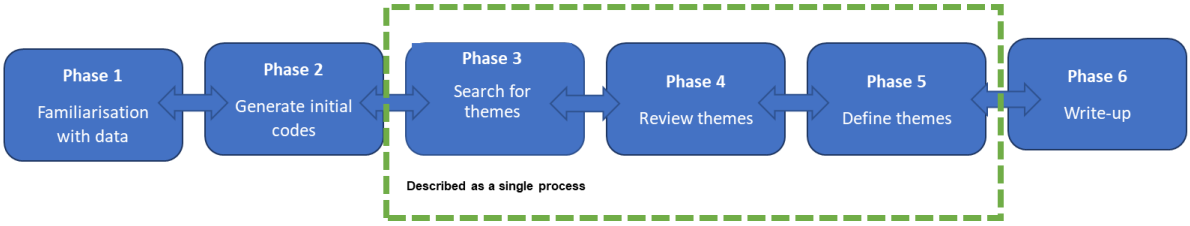


Figure 3.4 Braun and Clarke's six steps of data analysis.

Familiarisation with data (step 1) is described as *immersion* in the data (Braun & Clarke, 2013). The researcher sought to familiarise herself with the data through varying approaches. In the process, the interviews were conducted by the researcher and notes were taken immediately after the interviews, which gave the researcher a sense of her first impression of the data. The verbatim transcription of the interviews was produced by the researcher and the produced transcripts were read and re-read a number of times before initial coding was started.

Initial coding of data (step 2) was carried out by highlighting particular bits of data and assigning words or phrases which would remind the researcher why particular bits were found to be important (Braun & Clarke, 2013). The transcripts were formally coded using NVivo 12 software. The complete data set was coded which means *anything* and *everything* which was found relevant to answer the research questions. For this reason, the same transcript extracts were coded in as many ways as possible. The initial coding framework was checked for accuracy and completeness by one supervisor (ZB) and another researcher.

Searching for themes, review themes and define themes (step 3-5) as depicted in figure 3.4 these steps were conducted as a fluid process, and for simplicity these steps have been described as a single process. Once all the transcripts were coded, the generated codes were then organised into themes. A 'theme' is defined as *"a category identified by the analyst through her data*" (Bryman, 2012, p. 580). The themes were organised on three levels: overarching themes, main themes and sub-themes. The Nvivo12 mapping tool was used to create visual thematic maps (*see figure 3.5 and 3.6*). The thematic maps were a useful aid to identify duplicate codes or similar codes. Once the codes had been organised into a preliminary set of themes each theme was revisited and themes were merged or deleted where duplicate or overlapping themes were identified. During this phase it was sought to find themes which made sense on their own but at the same time, also would fit together to form an overall analysis or story from the data (Braun & Clarke, 2006). The refined themes and thematic maps were presented to the supervisors. Each theme was discussed and coded extracts were discussed with focus on ensuring that each theme was clearly distinct from each other (external heterogeneity). It was also assured at the same time, that the data within each theme was coherent (internal homogeneity) (Patton, 1990). This process was repeated during several repeated meetings where updated themes and thematic maps were presented. This was a lengthy and time-consuming process. One of the most challenging parts of the coding process was distinguishing between when the GPs were talking about the usefulness of NICE guidance in general and NG28. The final thematic map has been presented in chapter 4.

Producing the report (step 6) once the themes had been finalised the qualitative findings were written up as presented in chapter 4. The findings from the data analysis were supported by appropriate anonymised quotes from the participants. During the write-up of results the author has intended to provide extracts which "*illustrate/support an analysis that goes beyond their specific content, to make sense of the data, and tell the reader what it does or might mean*" (Braun & Clarke, 2006, p. 94). The write-up process was an integrated part of the data analysis, and as the findings and arguments were

coming together this was used as a final opportunity to remove or merge themes where duplicate and/or overlapping themes were identified. The descriptive content and interpretations are provided in chapter 4.

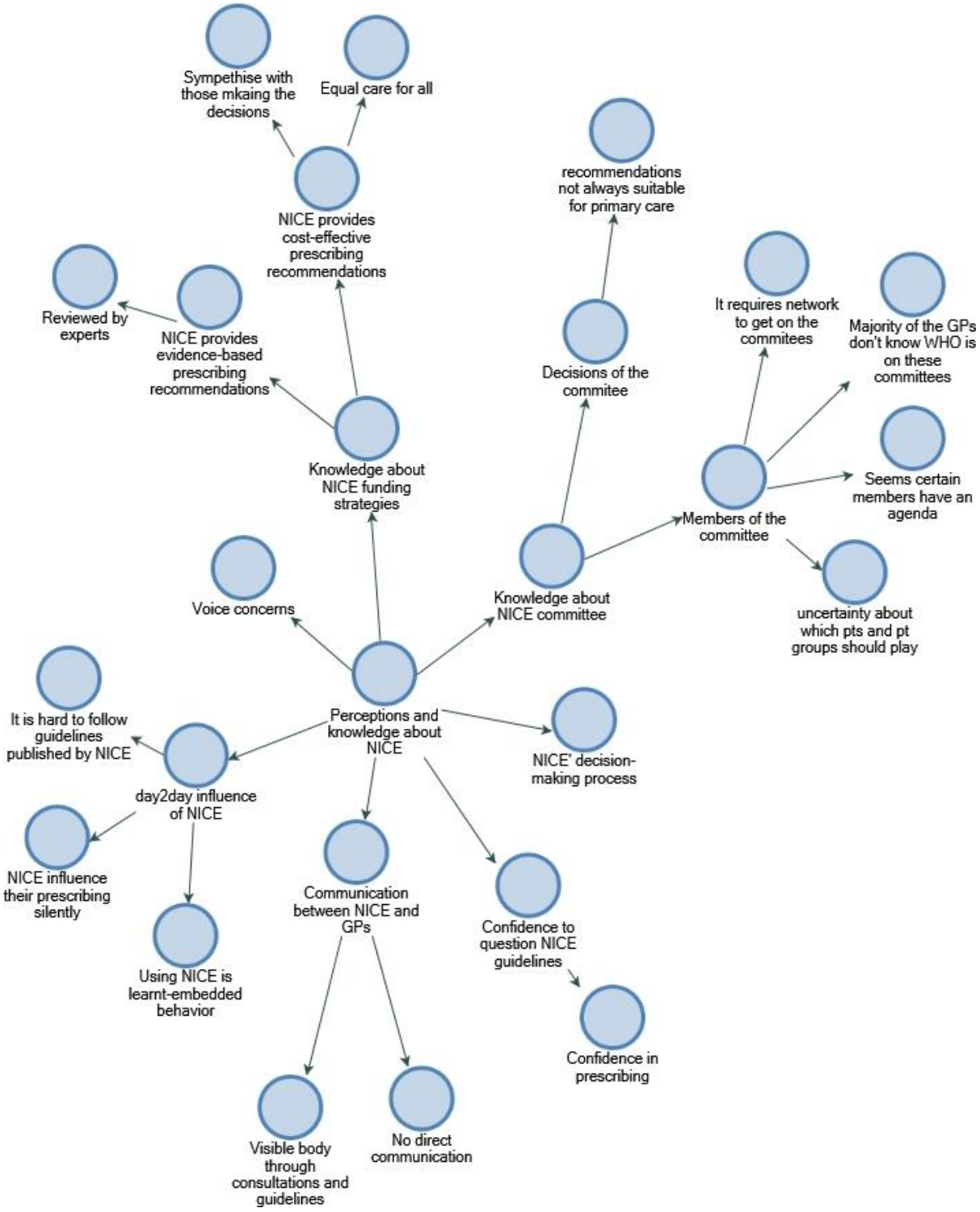


Figure 3.5 Example of thematic map developed during early stages of thematic analysis of the general practitioners' perception, knowledge and attitude towards National Institute of Care and Excellence.

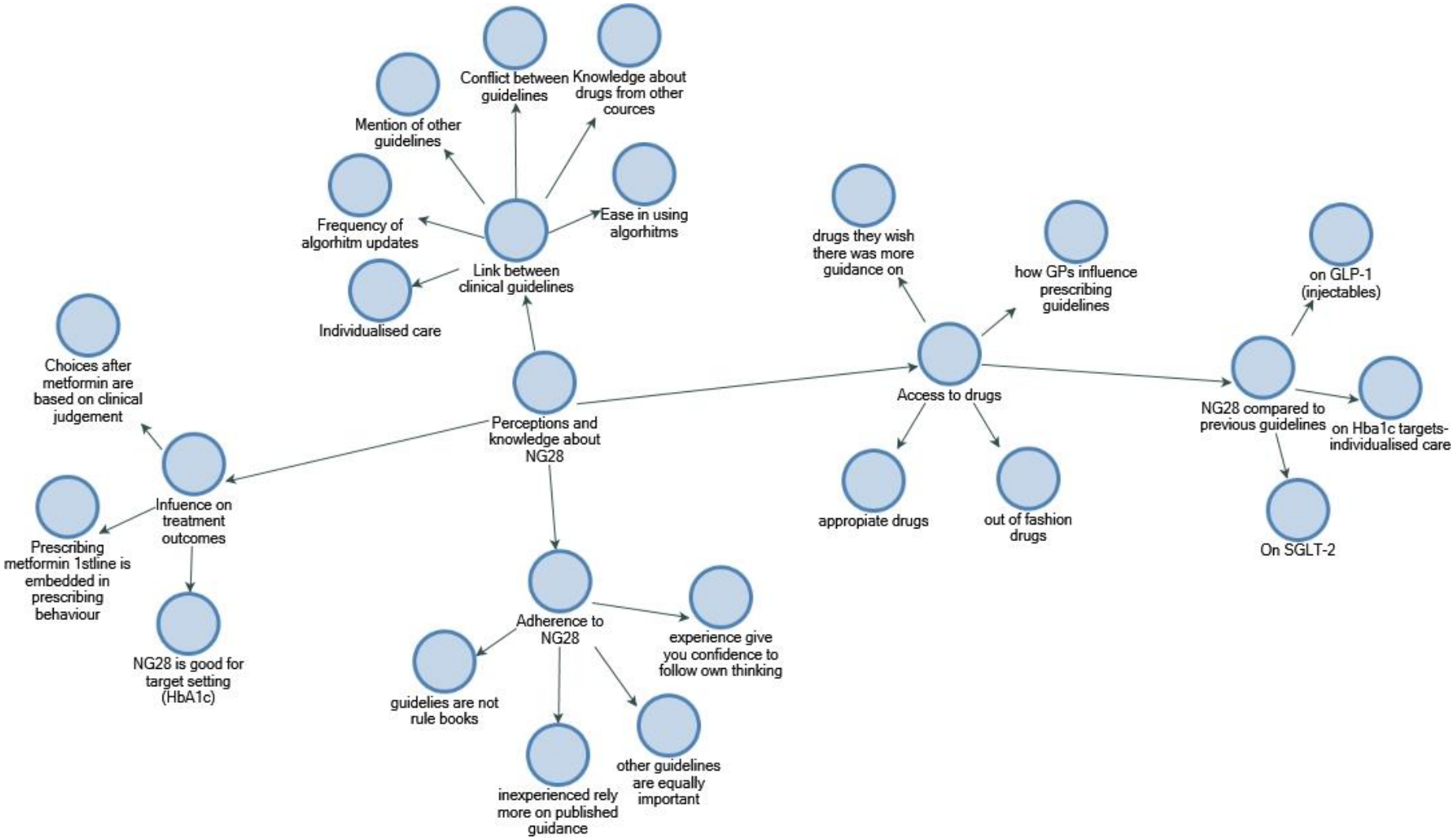


Figure 3.6 Example of thematic map developed during early stages of thematic analysis of the general practitioners' perception, knowledge and attitude towards the structure and processes of prescribing for patients with type 2 diabetes in primary care.

3.2.1.10 Rigour in qualitative reporting

Qualitative research methods have increasingly become an important contributor to health services research. However, the authors of qualitative research papers have been criticised for not emphasising enough on being rigorous and transparent in their reporting of findings (Nowell, Norris, White, & Moules, 2017). While the criteria for evaluating quality of quantitative research are commonly agreed on, the criteria applied on qualitative studies are not absolute (Cohen & Crabtree, 2008). The appropriate use of terminologies from a positivist paradigm such as *reliability* and *validity* in context of qualitative research are well-discussed in the literature (Lather, 1993; LeCompte & Goetz, 1982; Lincoln & Guba, 1985). The criteria from quantitative reporting seeks to develop generalisable data however qualitative researchers are interested in the *individual* meaning and experiences and hence does not seek to be generalisable (Yardley, 2017). In context of qualitative research this term has been replaced by the terms *trustworthiness* and *authenticity* when evaluating its worth. Lincoln and Guba et al. (1985) proposed the use of the following terms in qualitative research: credibility, transferability, dependability and conformability as qualitative techniques to establish *trustworthiness* (Lincoln & Guba, 1985). Further, fairness, ontological authenticity, educative authenticity, catalytic authenticity, and tactical authenticity were used as criteria to demonstrate *authenticity* of qualitative research (Lincoln & Guba, 1986). Creswell (2007) has suggested that to enhance *trustworthiness* any two strategies should be applied in qualitative research (Creswell, 2007). Below the strategies applied in study 1 are described: Triangulation was previously described as a mixed-methods strategy using multiple methods. Triangulation is widely used to ensure credibility and conformability of qualitative research (Creswell, 2007). As depicted in figure 3.2 the findings from study 1 were used during the development of the tool used in study 2. However, it should be noted that triangulation is not a tool to check validity of data and hence does not confirm whether the findings are true or false (Hadi & Closs, 2016). Dodgson (2019) states that reflexivity "*has been established as one of the ways qualitative researchers should ensure rigor and quality in their work; it is the gold standard for determining trustworthiness*" (Dodgson, 2019, p. 220). The researcher sought to describe her own understanding and pre-understandings which formed her initial understanding of antidiabetic medicines prescribing practices among GPs in primary care throughout the research process. The researcher kept a personal journal where she reflected on her observations. Here the researcher reflected on how the interview had gone; things or themes of interest mentioned during the interviews which were similar of different to other interviewees as well as things which the researcher wanted to explore further. This could for instance be when interviewees said that the American Diabetes Association- European Association for the Study of Diabetes (ADA-EADS) consensus report provided better more detailed guidance on how to prescribe than NICE. Further, the journal was also used to note down impressions or thought when reading literature and discussing her research with clinicians or researchers from the diabetes community. *Member checking* is also known as respondent validation as it refers to checking of findings and conclusions with interviewees from the qualitative study. As this study was a mixed-methods study the member checking included invitation to participate in the pilot study of the quantitative survey. The participants were asked to give written feedback on the pilot questionnaire which was based on the qualitative interviews and invited for on-to-one sessions (Polit & Beck, 2008). This is described in more details as part of

development of the survey tool in section 3.2.2.6. Of note, member checking does not judge accuracy of findings and hence does not ensure validity of the findings (Hadi & Closs, 2016). Throughout the research *peer review and debriefing* was carried out in multiple ways. First, the researcher had regular meetings with her supervisors (ZB and PT) during which an agenda for each meeting was presented with key findings, questions and reflections from the researcher. Following the meetings a summary report was produced detailing the decisions made and recommendations from the supervisors. The main supervisor (ZB) signed all the report electronically and was given the option to add further comments. Secondly, the researcher had meetings with a mixed-methods researcher to guide the research design and two diabetes experts to discuss the interpretations of findings. The purpose of these meetings was to ask clarifying questions and get guidance on the research based on their areas of expertise. Third, in the last year of research the researcher met every two weeks with a fellow PhD researcher to discuss research methodology, data analysis and interpretations (Nguyen, 2008). The purpose of these meetings was to exchange knowledge and experience from our individual research through discussion. Further, the researcher also engaged in presentation of findings and communication of her research with experts from the diabetes community. The researcher has sought to ensure transferability (Creswell, 2007; Long & Johnson, 2000) by providing a *rich and thick description* of the research through detailed reporting of study setting, participants, sampling technique, and data analysis in this PhD thesis. Further the researcher has sought to provide a detailed description of important aspects of the data collection (e.g. sample size, inclusion/exclusion criteria, interview guide, and data analysis) so the reader can make their own judgement of the transferability of the findings to other settings and situations.

3.2.2 Quantitative component: questionnaire survey

In the following sections the quantitative research method will be described by planning, developing research materials, collecting data and analysing the quantitative study (study 2). Where applicable alternative approaches considered will also be described.

3.2.2.1 Ethical approval

In first phase of the study SRIEC gave ethical approval for the data to be collected from GPs (appendix 6). However, as it was decided to expand the study to also include nurses and pharmacists another ethical approval was sought. The second phase of this mixed-methods study was approved by SRIEC on 25 October 2019 (REF: SAS-SRIEC-25.10.19-1, see attached appendix 16).

The participant information sheet (appendix 17) was made available so prospective participants could read the purpose of the study and potential benefits before giving consent to participate in this study. In the participation information sheet, the researcher explained the expected time commitment, assured absolute confidentiality of the information provided. For sampling purpose, a list of addresses of general practices in North West and North East & Yorkshire (Northern England) were obtained from NHS England (NHS England, n.d.-a, n.d.-b). To ensure anonymity and confidentiality, the questionnaires were not numbered prior to administration and hence it was not possible to link the returned

questionnaires back to the general practice. The retuned postal surveys were kept securely under lock and key.

3.2.2.2 Recruitment of participants

As described earlier it was initially planned to focus on GPs' views, perceptions and experiences with prescribing for patients with T2D. However, based on the findings from the qualitative findings it was decided to expand the participant group to include GPs, nurses and practice pharmacists. This choice was made based on the following observations. First it was clear from the interviews with the GPs that the care of patients with T2D is a result of collaborative efforts from multidisciplinary healthcare teams, and without exploring their views on prescribing practice a complete understanding of the subject could not be achieved. Although there is much research on multidisciplinary collaboration in primary care, there is limited evidence on how those team members collaborate in practice (Saint-Pierre, Herskovic, & Sepúlveda, 2017). Additionally, the diabetes experts had suggested to include all primary care clinicians in the first phase of the study but it had not been possible due to logistics. The following inclusion and exclusion criteria were used to screen the returned questionnaires:

Inclusion criteria:

- Currently registered as GP, nurse or pharmacist with relevant regulatory body.
- Currently working in primary care.
- General practice based in any CCG in the North of England.
- Any level of experience with treating patients with T2D.
- Willing to participate.

Exclusion criteria:

- Retired or stopped working in primary care.
- GP, nurse or pharmacist practicing in CCGs outside he North of England.

It was sought to maximise the chances of recruiting a representative sample of clinicians with varying experience in prescribing for patients with T2D. As it was anticipated that patients with T2D are treated by multidisciplinary healthcare teams it was decided to label the study packs "for the attention of diabetes healthcare professional 1, 2 and 3", respectively rather than naming a professional or intended recipient by name. By doing so it was intended that if more than one clinician in the general practice was interested in completing the survey they could do so. The initial questionnaires were sent out on 2nd September 2019, and additionally two reminders were sent out with two week gaps. The returned questionnaires were all collated and screened against the eligibility criteria once the survey closed. As there were no names on the returned questionnaires , these were given serial numbers in the order they were returned. None of the respondents used the slip to receive more information about the study findings.

3.2.2.3 Research sites

Similar to the qualitative study the sampling frame was CCGs in Northern England. According to the respective NHS pages at the time of the study there was 66 CCGs covering 2,342 general practices in the survey area *(appendix 14).*

3.2.2.4 Sample size

In an ideal world the whole population should be invited to participate in the survey. However, most surveys rely on a smaller sample size which is representative of the whole population (Oppenheim, 2000). To keep down the expense related to the sampling such as cost of printing and sending a survey pack including surveys, reminders and prepaid envelopes, it was not possible to collect data from all general practices in the survey area. It was decided to use a simple random sampling strategy for the postal survey. This form of sampling is considered to be a robust sampling framework where all participants has the same probability of being invited to participate (Oppenheim, 2000). As general practices receive many surveys via post, it is well-recognised that questionnaires tend to have a low response rate (Parahoo, 2014). As an attempt to overcome this challenge the researcher took following steps (Bruce, 2018, p. 156) :

- A cover letter was sent with the questionnaire explaining the aim of the survey and guaranteeing confidentiality of the responses.
- Two postal reminders were sent with two weeks intervals.
- The sample size was adjusted for non-response (*as described below*).

The sample size was calculated with a free sample size calculator provided by Creative Research Systems (Creative Research Systems, n.d.). The mechanism calculated the sample size based on the following criteria: n= 2,342; 95% confidence level and 5% confidence interval. The estimated sample needed to conduct this survey was calculated and was found to be 330 general practices. Non-response is a potential source of bias which should be considered when calculating sample sizes. It is estimated that a response rate of approximately a third is generally considered a good response rate (Burns & Grove, 2005). Based on this estimate it was decided to send three copies of the surveys (*addressed as described in section 3.2.2.2*) to each general practice during each round.

The general practices were randomly selected to be included in the survey. Research Randomizer, which is a free random number generator software (Urbaniak, 2013) was used to make the selection of general practices. The mechanism was fed with the following criteria; 330 sets of numbers with *one* number per set ranging from 1 to 2,342. Table 3.2 shows the numbers selected by the random number generator.

3.2.2.5 Recruitment

The initial survey packs were followed by two postal reminders which were posted at two week intervals. Reminders were sent out as there is a consensus that reminders boost response rates of postal surveys

(Smith, 2002). As the surveys were anonymised and did not collect identifiable information about the respondent and their general practice, it was not possible to trace the results back to the general practice and hence all general practices received the reminders. This was also explained in the modified participant information sheet which was enclosed with the reminders. The information sheet also encouraged the receiver to pass the survey on to other healthcare professionals within the practice if they had already answered the survey. The posted questionnaires were returned between 16th September 2019 and 31 October 2019.

Following the data collection 79 (24%) surveys had been returned with two or less responses from half of the CCGs in the survey area (n=79/330). In order to receive responses from more CCGs it was decided to boost the response with sampling through purposive sampling. An online survey link was created using the Qualtrics Software and was set to collect data between 5 November 2019 to 31 January 2020.

Table 3.2 Randomly selected numbers to receive postal survey using a random number generating mechanism.

624	31	2136	1259	1202	1597	2299	82	206	1110	1314
765	1368	1911	626	2281	2126	754	1251	631	1008	1793
2012	722	871	1011	2138	183	2242	850	1801	543	678
701	283	2179	2038	1964	1480	694	1661	497	1998	466
322	533	42	934	1138	1326	1611	1942	512	340	397
71	1445	1836	235	1473	109	1915	1133	1402	128	930
1244	994	1641	2146	2082	621	2243	521	1817	1047	225
1512	398	609	1594	1508	298	1396	621	439	1384	924
756	1853	2102	421	512	156	26	2225	1466	1431	1180
1899	257	94	1941	1535	92	23	1260	871	1810	1350
1335	893	180	358	1024	992	1224	2251	1374	672	1747
2116	2085	644	1117	424	1467	644	2114	1707	1960	731
1211	1563	1958	1784	792	1510	1149	349	664	291	1403
729	1235	1431	2108	273	45	837	49	1411	913	530
728	666	1144	144	1786	1403	246	1286	2289	1462	2339
2202	117	776	1480	1487	1980	184	1986	47	573	1044
1544	1215	1383	876	861	566	2162	2107	2044	1671	1389
263	2059	1786	997	1203	1425	187	862	1693	1692	1772
551	1276	2280	702	1265	115	1067	457	1355	155	2206
1346	2150	1456	2157	1915	1416	872	499	1046	1646	164
797	2039	612	1006	90	979	884	2207	1386	2195	1703
690	1189	751	141	984	1034	1688	774	355	1876	1116
204	1938	140	438	958	1750	1511	1686	838	2151	5
1658	1268	1369	2051	1435	63	406	211	2140	1820	2241
1063	1437	1990	1166	1165	1592	194	1403	1542	1197	410
997	500	599	1824	1872	2327	227	2037	1641	219	958
1574	735	99	578	2105	631	1013	1143	1411	169	1491
1335	1	101	1308	1313	1495	528	1828	318	2181	559
1618	2262	392	2057	1152	1824	2127	498	1542	107	1904
1855	1765	39	34	142	538	844	48	1563	2065	1620

3.2.2.6 Survey instrument

The development of a data collection instrument typically consists of four phases: defining the construct and content domain, generating items, pilot testing the scale, revising the scale, and finalising the scale (Burton & Mazerolle, 2011) . In the following section the development of instrument will be described.

Scope of data collection instrument

The initial draft questionnaire was informed by the literature and findings from the qualitative study. The literature review indicated that there was not any existing tool which quantified the step-wise approach to healthcare professionals' T2D prescribing practices in England. To ensure content validity the questionnaire was developed in collaboration with a research team. The aim was to develop a self-

administered questionnaire where the findings from the qualitative component were reflected in a true but sensitive manner. Additionally, the GPs from the qualitative survey were invited to pilot the questionnaire and answer some feedback questions regarding the developed instrument. As the aim of this research was to explore primary care clinicians' antidiabetic medicines prescribing practices it was important not only to generate a list of factors which influenced the healthcare professionals decision making but also to understand how elaborate the identified issues were. For this reason, the healthcare professionals were asked about their opinion on general statements as well as asked to describe their behaviour during hypothetical scenarios. The following questions were formulated to guide the discussion of the content of the data collection instrument:

- Which prescribing guidelines do primary care healthcare professionals use?
- How do primary care healthcare professionals manage adults with T2D?
- How common is insulin initiation in primary care?
- Which cost factors were considered when making antidiabetic prescribing choices?

Description of the data collection instrument

The initial draft of the questionnaire was carefully constructed based on the thematic analysis using statements from the transcripts. It is recommended that a questionnaire is no longer than 10-12 pages and does not take more than 20 to 30 minutes to complete. The initial draft of the questionnaire had 90 items divided across six sections. *Section A* collected demographic data on the respondents (sex, age, qualifications, prescribing status and name of local CCG). *Section B* was a 'tick all that apply' question regarding which clinicians are involved in antidiabetic medicines prescribing in the respondents' general practice. *Section C* consisted of binary questions concerning the respondents' use of prescribing guidelines. *Section D* were questions regarding the respondents' approach to clinical management of T2D patients. *Section E* contained binary questions concerning cost of antidiabetic medicines and finally *section F* had open-ended questions on multidisciplinary care teams. Additionally, the respondents were given the opportunity to write open-ended answers after each section.

The relevance of each item and question type was discussed with the supervisors. As the questionnaire was to be self-completed it was aimed to ensure that all questions were clear and unambiguous. The draft questionnaire was reviewed, modified and circulated several times before the researcher shared the draft questionnaire with two subject experts and one senior academic. Overall, the feedback on the draft questionnaire indicated that questions were appropriate and relevant to the findings from the qualitative study. A number of recommendations were given in regards to question type, length of questionnaire, phrasing and structure of questions all of which are important components when developing a questionnaire (Polit & Beck, 2016). It was for instance suggested to divide vaguely formulated questions into specific questions e.g. "*have you consulted any other guidelines/summaries such as your local CCG formulary*" was changed to two separate questions so the respondents were first asked if they had consulted ADA-EASD guidelines and then the local CCG formulary (appendix 18, section C). Questions regarding which healthcare professional the respondent would seek guidance from if they were in doubt about which medication to choose when treating a patient with T2D were first

asked so each available option was a separate question. The experts recommended that this detailed information would not add any value to the overall understanding of T2D prescribing practices, and changing those questions into “please tick as appropriate” would also help shorten the length of the pilot questionnaire (appendix 18, section D). This feedback was found useful as it is recommended that a self-completion questionnaire should not exceed 10-12 pages and should not contain any questions that are not really needed (Bruce, 2018). Other feedback was that a variability in language among healthcare professionals can result in different understanding of the questions regarding a step-wise approach to treatment. As phrasing is critical for the understanding of the respondent (Bruce, 2018) it was decided to adapt the wording from NICE, and ‘first- second- and third-line treatment’ was changed to ‘treatment initiation, first and second treatment intensification’ (appendix 18, section D). Lastly, it was suggested that the open-ended feedback questions after each section were removed as these would be difficult to code for data analysis, and hence would not add valuable information different from what is known from the interviews (Bruce, 2018). Further, some suggestions were made in sentence structure to improve clarity of the items. The suggested changes were taken under consideration and the author discussed these with the supervisory team. The administered pilot questionnaire was five A4 pages long, consisted of the six themes described above and included 64 items which were numbered sequentially (appendix 18).

Testing the data collection tool

Pilot study is a key stage of development where the data collection instrument is tested on a small sample before the main study is conducted (Parahoo, 2014). The primary aim of piloting the questionnaire was to check if the respondents understood the questions in the same way, questionnaire sequencing was appropriate and if all instructions were clear. Lastly it was important to check if the questionnaire had an appropriate length.

Piloting is also an opportunity to check the validity and reliability of a questionnaire (Jones & Rattray, 2010). Face validity was evaluated by pre-testing the data collection tool on two PhD researchers who are pharmacists by profession. The feedback from the pre-test indicated that the questions appeared to be relevant, clear and easy to understand.

As study 2 complements and expands on the findings from study 1 (*see figure 3,3 for flow diagram*) it was found appropriate to ask participants from the qualitative interviews if they would be willing to participate in the pilot study. The number of GPs in the qualitative sample was also appropriate for a pilot sample size which estimated to be between 20 and 50 participants (Bruce, 2018). This way the final sample would not lose potential respondents (Bruce, 2018). All the interviewees from study 1 had given their consent to be contacted for the pilot study and had provided contact information. The sample consisted of 23 GPs from the qualitative interviews. Additionally, two practice pharmacists from the target population were purposively recruited for the pilot study.

As it was anticipated it would be difficult to engage the respondents in one-to-one feedback sessions the participants were debriefed by asking eight open-ended feedback questions following the last page of the questionnaire (table 3.3). The questions were regarding if the questionnaire reflected the topics discussed during the qualitative interviews and to check for problems and issues with filling the

questionnaire. The feedback questions were used to modify the findings after the pilot survey was closed.

Table 3.3 Feedback questions which were asked during pilot testing

Question 1	**The posed questions and options allowed me to describe which staff is involved in the treatment of patients with type 2 diabetes fully.** *Please provide feedback on if you were able to give a full description based on the available options.*
Question 2	**The questions in section C covered all the problem areas with current NICE diabetes prescribing guideline.** *Please feel free to mention any issues not covered.*
Question 3	**The available options Q36, Q37 and Q38 covering the clinical management of an adult with type 2 diabetes allowed me to describe my step-wise approach.** *Please let us know if the given options limited your response in any way.*
Question 4	**The questions on NICE 2015 guidelines cover the problem areas with current prescribing guideline which I mentioned during the interview.** *Please provide us with examples of themes which you find we have now covered.*
Question 5	**The available options in Q61-Q73 allowed me to describe when and how I communicate with other healthcare professionals when making clinical decisions about treatment of patients with type 2 diabetes.** *Please provide feedback on if you were able to give a full description based on the available options.*
Question 6	**The questions Q79-Q85 describes the role my local CCG play in my daily prescribing in regard to reducing cost.** *Please provide us with examples of themes which you find we have now covered.*
Question 7	**The questions were clear and easy.** *Please provide us with examples of unclear questions or questions with limited response options.*
Question 8	**The posed questions did not make me feel judged/under scrutiny.** *If this is the case we apologise in advance, please let us know so we can avoid this in future.*

Distribution of pilot questionnaires

Piloting was also used as opportunity to test the planned questionnaire distribution method and it was intended to follow the planned procedure. The pilot study pack was posted to the participants between July and August 2019. The survey pack included a letter of invitation (appendix 17) intended for gatekeeper/ participants explaining the potential importance of the project and a 5-page survey (appendix 19) and an addressed and prepaid envelope to mail the survey back to the researcher. There was minor difference between the pilot survey pack and final survey pack: The pilot invitation letter invited participants to re-test of the questionnaire, fill the feedback question in as much detail as possible and asked if they would be willing to give one-to-one feedback over the phone. The pilot study was addressed personally to the GPs and practice pharmacists and sent to the provided addresses. Reminders were posted out to the general practices two and four weeks after the initial study packs were sent, respectively. The three posted study packs contained the exact same documents and instructions each time. In the reminders, the requested completion dates were changed and additionally, a note was enclosed to explain that due to anonymity it was not possible to exclude those who had already responded to the questionnaire. Those who had already responded or were not interested in participating in the study were asked to ignore the reminder. The respondents were requested to complete and return the questionnaire within fourteen days of receipt using the enclosed prepaid envelope.

Data entry and analysis of pilot study

Data from the retuned questionnaires were entered into Microsoft Excel (version 2008). Descriptive analysis on gender, age, years of experience in primary care, prescribing status and the name of the local CCG was included in the analysis. The feedback questions were also entered into Microsoft Excel

(version 2008) and descriptive data analysis was undertaken. Cronbach's α value of the pilot questionnaires was used to measure the internal consistency (reliability) of the survey.

3.2.2.7 Modifications based on pilot study

Feedback from general practitioner sample

The response rate from the pilot sample was 43% (n=10/23). The feedback questions were answered by all the respondents (n=10). The preliminary analysis of responses showed that the respondents had answered most of the questions. A limited response to section F regarding interdisciplinary care was noted. The GPs found that all major themes from the qualitative interview were reflected in the questionnaire. The following feedback was received regarding the content of the piloted questionnaire: One GP found that the questions did not fully capture their prescribing style as they did not follow 'rigid' guidelines after their many years of experience in primary care. Two GPs wrote that depending on patient circumstances they would waiver from the described step-wise approach. As mentioned earlier in this chapter, this feedback was already anticipated and for this reason a simple situation was described where the respondents were asked to indicate their preferred choices of drugs when comorbidities/ contraindications/patient preference were not an issue (table 5.1, feedback question 3). It was observed that some of the questions on insulin prescribing (table 5.1, feedback question 4) needed to be rephrased and others deleted as they were not relevant to all participants. Moreover, three GPs pointed out that they were encouraged by their CCGs to use medicines with lower acquisition cost unless there was a clinical reason for using an expensive medicine (table 5.1, feedback question 6). This was similar to the findings in the qualitative study. Only one of the GPs agreed to participate in the one-to-one session. None of the GPs agreed to participate in the retest of the pilot study after completing the draft questionnaire.

Feedback from practice pharmacist sample

There were several gaps in the responses from the practice pharmacists and these were explored. None of the practice pharmacists answered the feedback questions.

Both practice pharmacists gave consent to participate in the one-to-one session after completing the questionnaire. During the one-to-one session they explained that they had left the feedback section blank as there were a number of questions which they were uncertain about and wanted to discuss in the one-to-one sessions. Questions 1 to 10 (appendix 18: pilot questionnaire) related to 'about your practice' were left blank as they were perceived to be vague. One practice pharmacist had left all the questions on 'step-wise approach to treatment' blank. The practice pharmacist explained that the lead diabetes GP or nurse in their practice would often asses the patient and they would let them know which medicine to initiate the patient on. The practice pharmacist further emphasised that the prescribed drugs would be chosen by the GP or nurse and for this reason, this is not necessarily a reflection or their own preferred drug choice. When the pharmacists were asked why they had only answered section F with a few words, it was explained that they found the questionnaire to be lengthy.

Overall modifications based on the pilot study

Based on written and/or oral feedback from 10 GPs and 2 practice pharmacists, the questions were reviewed, and the questionnaire was redrafted by the researcher and discussed with the supervisory team. Minor linguistic corrections were made to the participant information sheet. The order of questions was changed and some questions which were initially binary ('yes'/'no') questions were changed into list options which could be ticked (multiple choice). Questions 1 to 10 were rephrased so they were relevant to all healthcare professionals regardless of their prescribing status. Based on one-to-one sessions and sparse responses on *section F* from GPs and practice pharmacists in the pilot study it was assessed that it was not of the essence of the project to understand the dynamics of the healthcare professionals involved in the care of patients with T2D. Therefore, these questions were omitted from the questionnaire. Lastly, the slip where the clinicians could provide their email address to receive the published findings was adjusted to fit the margins so the text on the previous page was not cut off when separating the slip from the survey.

After making the recommended changes the two practice pharmacists filled and returned the modified questionnaire four weeks after the one-to-one sessions. In the retest the number of 'blank' and 'unsure' responses were changed to 'yes' or 'no' for 5 and 13 questions, respectively. The Cronbach's α value was calculated based on the responses (n=2) showed an overall good reliability of the pooled survey questions (table 3.4). All questions types are not subject to an intercorrelation test and hence only questions related to each other were checked for intercorrelation (Polit & Beck, 2008).

Table 3.4 Cronbach's alpha for pooled survey questions.

Question number	Cronbach's alpha
Demographic questions	*Not relevant*
Question 1 to question 2	*Not relevant*
Question 4 to question 8	*Not relevant*
Question 9 to question 13	$\alpha = 0.958$
Question 14 to question 15	*Not relevant*
Question 16 to question 18	*Not relevant*
Question 19	*Not relevant*
Question 20 to question 23	*Not relevant*
Question 24 to question 27	$\alpha = 0.757$
Question 28 to question 29	$\alpha = 1.000$
Question 30 to question 31	*Not relevant*
Question 32	*Not relevant*
Question 33 to question 37	$\alpha = 0.976$
Question 38 to question 39	*Not relevant*
Question 40 to question 45	*Not relevant*

The revised draft questionnaire was shared with the two diabetes experts along with the feedback questions described in table 5.3. The two diabetes experts provided feedback on the draft questionnaire and one-to-one sessions were held with them to discuss any further amendments. The experts advised that no further adjustments of the questionnaire items were necessary.

Final questionnaire

The final questionnaire was four A4 pages long and consisted of 45 items. The purpose of the questionnaire was to measure primary care healthcare professionals' T2D prescribing practices. During the development of this questionnaire it was important to the researcher that the instrument could be applied in primary care practice to investigate findings from the qualitative study which needed further clarification. Researchers are encouraged to make the final choice on format for measurement based on the intended of use and the nature of the variables being measured (Curtis & Drennan, 2013). Three basic question types were used: *dichotomous scales* ('yes' / 'no'/'unsure') are useful for precise data and were used when the intent was to confirm/affirm statements regarding attitude, knowledge and experiences identified in the qualitative study. The disadvantage of using this question type is that it doesn't allow the respondents to add nuance to their answers. The *5-point Likert rating scale* was used for declarative statements when the intent was for the respondent to express their opinions, beliefs and attitudes (Jones & Rattray, 2010). The limitation of using a scale to measure attitudes is that it reduces the richness of their response to a number (Curtis & Drennan, 2013). *Multiple choice* (single response and multiple response) with a single response was used for demographic questions (sex, age, years of experience etc) and where it was intended to get descriptive responses.

3.2.2.8 Data collection

The postal surveys were distributed as explained in the pilot study in section 3.2.2.5 The questionnaires were self-administered by the healthcare professionals.

The online survey was distributed on social media (Facebook, LinkedIn and Twitter) and within this researcher's personal network. Anyone who was available and willing to take part in the survey could click on the link.

3.2.2.9 Data management

The data from the postal questionnaires was entered using Microsoft Excel (version 2008). As GPs, nurses and pharmacists had entered various professional degrees it was decided to code "qualification" as "profession". It was found that this would not impact the data analysis as it was not intended to compare the differences within the professions. The data entries in Microsoft Excel were also checked by a second researcher.

The online questionnaire responses were exported to Microsoft Excel (version 2008) using the built-in export function in Qualtrics software. The responses were screened by SR and a second researcher individually and responses from CCGs outside the defined survey area were excluded. The remaining data entry procedure was similar to that of the postal survey.

3.2.2.10 Data analysis

Only valid responses were subject to analysis. Data analysis was conducted by the researcher using IBM SPSS Statistics for Windows version 26.0 and was overseen by the supervisors. Independent sample t-test was used to determine any significant differences between those who completed the

postal survey versus those who completed the online survey. No differences were observed between the two groups (p>.05) and the data were combined and analysed as one cohort.

Item non-response in the categorial data was treated as missing data for all items except from 'gender' where a missing response has been interpreted as 'prefer not say'. Missing data were not adjusted for with imputation or weight adjustment methods (Brick & Kalton, 1996). The data was analysed with the Chi-Squared test to determine association between the scales and categorical data (age, profession, years of experience in primary care and prescribing status). Categories from the five-point Likert scale were combined to create a three-point scale. For the purposes of clarity, the three-point scale has been presented in this thesis, together with the results from the chi-squared test. *P value* <0.05 was considered to be statistically significant.

3.2.2.11 Validity and reliability in quantitative research

Face validity, content validity and construct validity

A questionnaire should measure all aspects of the topic being studied. Face validity and content validity are the two most commonly components of validation of the instrument described in the literature (Parahoo, 2014). Polit & Beck define validity of a questionnaire as the degree to which a data collection instrument measures what it is intended to measure. Face validity checks if the questionnaire seems to be measuring the described concepts (Bruce, 2018). In the current study this was assessed by carrying out a pre-test (n=2) to see if the formulated questions appeared to be relevant, clear and easy to understand (Jones & Rattray, 2010). Content validity is carried out to ensure that all relevant aspects of the topic is investigated and irrelevant questions are omitted (Parahoo, 2014). For this reason a research team with different backgrounds were consulted as experts throughout the mixed-methods study. This test is based on judgement and no objective methods of assessment exists hence subject experts who had previous experience with T2D prescribing practices in primary care were consulted. Further, the GPs from the qualitative study were debriefed as described in section in section 3.2.2.6 on instrument development.

Reliability

During questionnaire development, reliability refers to the accuracy of measurement (Parahoo, 2014) and often focuses on stability and consistency (Polit & Beck, 2016). Reliability is measure of the instrument's ability to yield the same results when it is re-administered under the same conditions. While reliability is vital it is not sufficient to assess validity of a tool on its own. The stability refers to the degree to which same results are produced when being administered twice. In the current study the pilot sample was invited for test-retest and carried out as described in section in section 4.2.2.6 on instrument development. The internal consistency of the developed questionnaire was checked by using Cronbach's alpha. In the current study a Cronbach's alpha value of >0.7 was deemed acceptable (Polit & Beck, 2016). The limitations of the survey tool are discussed in section 7.4.3.

3.3 Reporting of the mixed-methods study

This section describes how and when the findings from study 1 and 2 were integrated. This section also briefly describes the quality criteria used during the research.

An important aspect of planning and conducting mixed-methods research is to give consideration to when and how the data will be integrated (Venkatesh et al., 2013). While planning this research the researcher has given much thought to ensuring the credibility of the research and how to express this within the study. As depicted in figure 3.2, the two studies were integrated during the development of the tool used in study 2. According to Farmer and colleagues, triangulation of findings increases the validity of findings and enables the researchers to compare multiple perspectives on the research question (Farmer, Robinson, Elliott, & Eyles, 2006). Nevertheless, it is important to be aware that conflicting results may be found, and there is not yet any consensus on how to interpret results if this scenario arises(Ross, 2012).

Although it is commonly agreed that health services research should be reported transparently (Creswell, 2007; O'Cathain et al., 2008) there is still a lack of consensus on how to report mixed-methods research (Hadi & Closs, 2016; O'Cathain et al., 2008). The existing guidelines and frameworks all aim to improve the quality of reporting (Hadi, Alldred, Closs, & Briggs, 2014; NIH Office of Behavioral and Social Sciences, 2018) and hence it is the researchers' responsibility to appropriately validate the mixed-methods research design. The key elements in the quality in reporting frameworks are to *'justify the used methods approach, describe the mixed methods design (priority, purpose, sequencing and stage of integration), describe the used methods (sample size, data collection and analysis), describe how, when and where integration has occurred and identify limitations related to the applied research design' (Ramzan et al., 2019a).*

This study was appraised using the checklist (table 5.3) for Good Reporting of a Mixed Methods Study (GRAMMS) as described by O'Cathain, Murphy and Nicholl (O'Cathain et al., 2008). The researcher found that the criteria encouraged transparency about the role of the individual component in the mixed-methods research design as well as how data and findings from the two distinct studies were integrated. The checklist criteria have been outlined in table 3.5, and their application has been indicated.

Findings from sub-studies 1-3 are contrasted and compared in section 7.2 and then discussed in context of the existing literature (section 7.3.1). Further, as the quantitative tool was not fully validated (discussed under strengths and limitations in *section 7.4.4*) it was considered appropriate to answer objective 2 and 3 based on findings from the qualitative study.

Table 3.5 Good Reporting of a Mixed Methods Study (GRAMMS) checklist.

Guideline criteria	Remarks from researcher
Describe the justification for using a mixed methods approach to the research question	Rationale for choosing mixed-methods design described in section 3.1.1.4.
Describe the design in terms of the purpose, priority and sequence of methods	Purpose, priority and sequency of methods have been described under justification for choosing exploratory research design (section 3.1.1.5).
Describe each method in terms of sampling, data collection and analysis	Qualitative methods have been described in section 3.2.1 and quantitative methods have been described in section 3.2.2.
Describe where integration has occurred, how it has occurred and who has participated in it	Has been described throughout chapter 3, and section 3.3.
Describe any limitation of one method associated with the present of the other method	Strengths and limitations of combining the methods have been described in section 7.4.
Describe any insights gained from mixing or integrating methods	The findings from the three sub-studies have been discussed in section 7.2 under general discussion of key findings.

CHAPTER 4

Study 1: General practitioners' beliefs and behaviours influencing antidiabetic medicines prescribing practices in Northern England

4.1 Introduction

Current study is an exploratory study which applies qualitative methods as described in chapter 3. The primary aim of the qualitative phase was to explore the management of adults with type 2 diabetes (T2D) in primary care through the experiences of general practitioners (GPs). This chapter states the aims and objectives of the qualitative study followed by the findings. The chapter concludes with a reflective summary which is structured according to below-stated research questions.

4.2 Aims and objectives

The aim of this study was ***to explore perception, knowledge and attitudes*** regarding primary care GPs' antidiabetic medicines prescribing practices in primary care. The specific questions were:

1. **What is the perceived value of NICE in clinical practice?**
   - 1.1 What is the perceived value of the guidelines which are published by NICE?
   - 1.2 How do the GPs perceive the evidence provided by NICE?

2. **How useful is NG28 when making prescribing decisions during day-to-day prescribing?**
   - 2.1 Do the GPs use the NICE guidelines on T2D management (NG28) during their day-to-day practice?
   - 2.2 What influences their prescribing decisions?

3. **How do the GPs choose between antidiabetic medicines when treating patients with T2D?**
   - 3.1 Which changes have the GPs observed in their prescribing practices?
   - 3.2 Which drugs do GPs prescribe at treatment initiation, first and second intensification?
   - 3.3 Which factors do GPs consider when choosing between drug classes?
   - 3.4 Which organisational factors influence the GPs prescribing decisions?

The aim of conducting face-to-face interviews was to get an in-depth understanding of how antidiabetic medicines prescribing for patients with T2D was carried out in primary care. The data analysis was based on 21 interviews and resulted in the generation of four overarching themes, and multiple subthemes (figure 4.1). The findings within each theme are described distinctly however during the interviews they were often weaved into each other.

The GPs who participated in the interviews indicated that they had different degrees of engagement in policy and practice decisions within T2D. The participating GPs who treated fewer patients with T2D often made use of prescribing guidelines as compared to participating GPs who more frequently treated patients. Some participants had specialist interest in diabetes and were involved in developing the local CCG guidelines. For this reason, the term "experienced" is used as the GPs own definition of being experienced with antidiabetic medicine prescribing for patients with T2D, and hence it does not refer to

the number of years they have been in practice unless it is explicitly stated. The terms 'cost' and 'price' are used interchangeable by the interviewees and must interpreted in context of the presented quotation. Additionally, the price of antidiabetic medicines has been found to be a factor which is present across all themes and for this reason these findings have been presented in the relevant sections.

4.3 Results

4.3.1 Participants

In this study, 21 interviews were conducted. The characteristics of the interviewees are presented in table 4.1. The distribution of males and females was almost equal (52% males versus 48% females) and the age ranged between 30 years and 59 years. One participant was a registrar GP and the remaining participants had between 3 months and 34 years of experience in general practice. The mean length of the interview was 27.6 minutes. The participants own description of their experience with prescribing for patients with T2D have been used to classify them as low, medium and highly experienced with antidiabetic medicines prescribing,

Table 4.1 Participant characteristics

ID	Age (years)	Gender	Years of experience in GP surgery	Length of interview (minutes)	Experience with antidiabetic medicines prescribing*
Interviewee 3	38	Male	6	38	Low
Interviewee 4	39	Male	10	43	Medium
Interviewee 5	47	Female	16	26	Medium
Interviewee 6	55	Male	21	56	High
Interviewee 7	42	Male	14	24	Medium
Interviewee 8	38	Female	4	35	Medium
Interviewee 9	46	Male	13	57	High
Interviewee 10	41	Male	8	15	Medium
Interviewee 11	33	Female	4	17	Medium
Interviewee 12	47	Female	16	35	Medium
Interviewee 13	28	Male	Registrar GP (18 months)	27	Low
Interviewee 14	58	Male	14	18	Medium
Interviewee 15	57	Male	30	16	Medium
Interviewee 16	43	Female	4 months	18	Medium
Interviewee 17	58	Male	14	25	Medium
Interviewee 18	54	Female	27	23	High
Interviewee 19	38	Female	6	22	Medium
Interviewee 20	44	Male	16	22	Medium
Interviewee 21	43	Female	5	25	Medium
Interviewee 22	43	Male	7	15	Low
Interviewee 23	44	Female	17	23	High

*as per general practitioners' own description of their experience with prescribing for patients with type 2 diabetes.

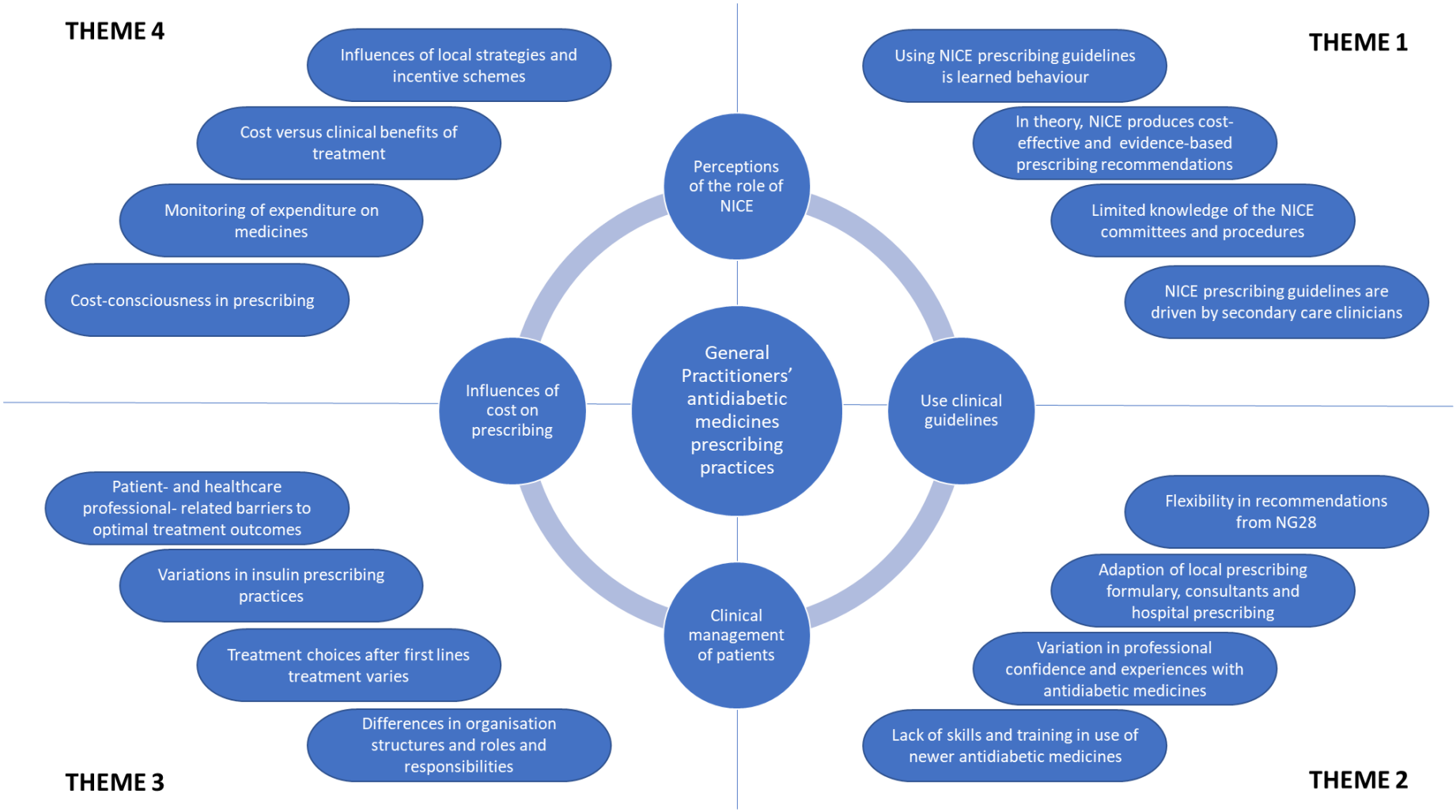


Figure 4.1: Diagram of themes illustrating connectivity and overlap of themes.

During the qualitative interviews beliefs and views from GPs working across twelve Clinical Commissioning Groups (CCGs) in Northern England (figure 4.2) were presented.

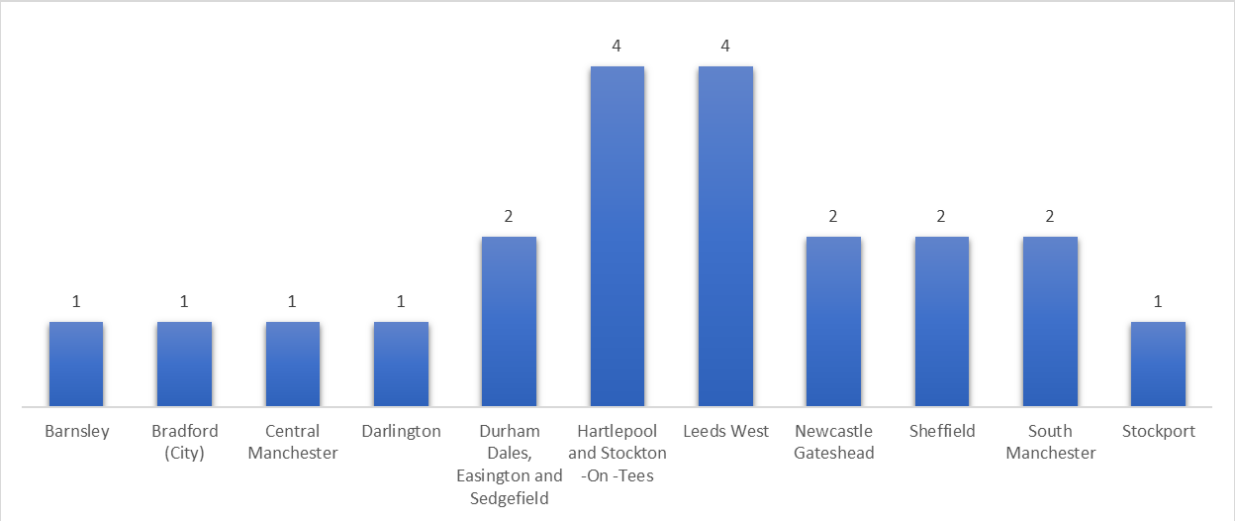


Figure 4.2 Clinical Commissioning Groups

4.3.2 Role of NICE in clinical practice

This section presents the GPs general beliefs about the role of NICE in clinical practice and the overall influences on prescribing in primary care. Further, the GPs knowledge and beliefs about the Guideline Development Group (GDG), clinical expertise of the GDG members and views of the reviewed clinical trial evidence are presented in turn.

4.3.2.1 Value of NICE recommendation in the healthcare system

The GPs found that the use of NICE prescribing guidelines is a learned behaviour as they have been using NICE guidelines since their early medical training

I think we are encouraged, especially with trainees... with exams to follow NICE. [P13]

I guess parts of it, is my age and my training. [P18]

The clinical guidelines produced by NICE are perceived to provide direction for clinical choices but do not preclude clinicians from using their own clinical judgement. GPs also said that times have changed and it is acceptable to gather knowledge from other means than NICE.

10 years ago, everyone referred to NICE without question whereas now, I think, people are looking at other guidelines as well. [P21]

GP22 similarly reported that it is considered good practice to be aware of all available guidance.

I will be honest but because it is more or less in our second nature [inserted: to use NICE prescribing guidelines]. It is good practice to be aware of most guidelines. [P22]

The GPs generally recognised that it must be difficult to sit on the Guideline Development Group (GDG), and be the one who decides which treatments should be included in the prescribing guidelines. GP7 expressed appreciation that someone is willing to take on the task of deciding which treatments should be recommended and which should not.

…as an ethos, I think it is absolutely right what they do. Really, to try and evaluate whether something is cost-effective for looking at a population level. So yeah very much needed. [P7]

Likewise, GP15 found that NICE makes prescribing decisions that benefits the overall healthcare system.

I will not criticise them. I would say that they are working for the best of the patient and the best for the economy system and the country. That is it. [P15]

GP3 described NICE as being good quality and cost-effective healthcare but not necessarily excellent healthcare as the recommendations from NICE are constrained by the cost of the treatment.

I am not sure they are excellence-centred because everything they do is supposed to be cost-effective, is it not? So, cost-effective, good quality healthcare as opposed to excellent health care. [P3]

This view of NICE is shared by GP4 and GP7:

So, I do believe NICE is a force for good but unfortunately, they are constrained by finance… [P4]

What is their purpose? It is to save money essentially or have a cost-effective healthcare system. [P7]

Two GPs pointed out that NICE was established with the intend to omit the geographical differences in prescribing.

…there was such a spectrum of change, it was a real postcode lottery is to what treatment you would get… [P8]

NICE gives national guidance and therefor, in theory, should avoid postcode prescribing depending on their affordability within different regions of the country. [P9]

GP9 further adds:

The value, in theory, is meant to be good and everybody therefor follows it, so you get a universal approach. [P9]

GP8 found that NICE gives a safety network which the participant can fall back on if something goes wrong.

I think medically, legally and ethically if something goes wrong or something is missing you can say.

"*Well, there is no right answer, so this is the guidance, I follow the guidelines"* [P8]

The GPs were aware that the health budgets are limited, and it is necessary to allocate healthcare resources so the most people can get treated. GPs said that they have a duty of care to the patients but also an obligation to spend responsibly.

I think, that at a population level we have to think about cost because there is not an unlimited budget but equally for the person sitting in front of you, I think, it really is what works for them… [P23]

The study showed that the GPs believed that responsible spending did not necessarily equal prescribing low cost or cheaper generics. GPs believed that prescribing an expensive drug which could reduce HbA1c levels and had other added benefits were long-term economic investments in the patient' health which potentially could prevent future hospitalisations.

They may have had a hospital admission because of the hypoglycaemic attack that you could have avoided so there is a bit of an art to it really, and sometimes NICE does not seem so sympathetic really. [P6]

If you are reducing those hospital admissions, you are saving money in the NHS. [P9]

This view was shared by other GPs who similarly described complications and hospitalisations following uncontrolled blood glucose levels to be more costly to the NHS than the disease itself.

I think good care costs money and the consequences are to bigger complications and certainly they are expensive. [P9]

…if you are looking at it purely from a business point of view the cost of the complications are going to be much greater probably than the cost of any medication. [P21]

We know that in an individual patient, if we can help them to have HbA1c which is in the right range, we reduce the risk of complications which are extremely costly. [P23]

Knowing that the recommendations from NICE are based on critically appraised evidence gives them confidence to apply it in practice without questioning the validity of the recommendation.

It gives me the confidence of prescribing to patients because it has been well-researched. That is why I am able to hand over that script quite confidently and also letting them know of the side-effects… [P16]

…there is probably some huge number of research trials that have been done, that have influenced this decision or there has some big financial decision that if you were to rule it out country wide, then it would break the bank. [P6]

In summary, the interviewees have a shared understanding that NICE' role is to ensure uniformity of healthcare provision. They appreciated that their recommendations were based on cost effectiveness and scientific evidence which was appraised by clinical experts.

4.3.2.2 Knowledge about the NICE guideline development groups

The majority of the GPs did not know *who* is on GDG who produces clinical guidelines. GPs expressed uncertainty about if the selection of committee members was a transparent process. Several GPs believed that that the clinicians on the NICE committees were an "old boys' network".

I think that there is probably got a lot of conflicts of people that sit in the panels [P5]

It feels a little like an old boys' network and it does not feel like there was an interview process which was open to everybody [P9]

The participants found that although NICE advertised the consultations the recruitment process to become a part of the GDG was not fair to those without contacts within the diabetes network. GP12 tells how the participant e once was approached by someone to become a part of the I GDG merely by coincidence and not because the participant was seeking to become involved in the NICE committee:

…that was only through happens stance. I just happened to be in that group, and he happened to be a person who was a patient representative who then happened to say, "there is a gap for a GP" [P12]

Although the GPs do not always find the guidance suitable for primary care, they do not question the clinical expertise of the committee members involved in the production of the guidelines. The recommendations are found to be based on a combination of clinical experience of the committee members and scientific evidence.

…a group of experts who have got experience in that field, and who have spent time researching all the current evidence to give us something that is reliable. [P12]

…the NICE guideline is not produced by one person. It is a group of people so there is evidence. Based on experience based on thoughts of other people. [P17]

I think there should be stronger input particularly from primary care because of you talking about type 2 diabetes in the UK, that means primary care delivering nearly all of it probably about 80-90% of patients will be managed in primary care. [P9]

Some GPs expressed doubts about the evidence which evidence had gone into the guidance. They shared that there is anecdotal evidence that prescribing recommendations at times are driven by influential members of the GDG' personal agenda rather than scientific evidence.

It seems to me that they must have been lobbied by somebody with some of the decisions that they make. [P18]

GP6 for instance mentioned that they did not understand why repaglinide was in the draft guideline

Though I think, that originally the latest guidelines it was somebody who is high up who wanted that [inserted: repaglinide] to feature in the guidelines and I think…that seems a strange thing to do. [P6]

Similarly, GP12 talks about how repaglinide was mentioned in the draft guidelines but then removed again after the consultation. The participant further added to never have prescribed repaglinide for patients due to concerns about patients' adherence to the dosage regimen.

… when they put out the draft guideline, we had repaglinide in there, and people were not keen but, because I think, you have to take it often. It is never a drug that I have ever used before… [P12]

In summary, the GPs had varying views of the transparency in the selection of committee members. The balance between evidence and clinical experience in the recommendations was questioned.

4.3.2.3 Beliefs about the decisions of the NICE Guideline Development Groups

There was a mixed perception of the communication between NICE and GPs. The majority of the GPs reported that they do not have any direct communication with NICE. Others reported that they find NICE to be visible through consultations and published guidelines.

I think, once they have published guidelines they are always very visible. […] And also, they do usually produce their draft guidelines for people to comment on, which I think, is a positive. So, there is an opportunity to get involved [P23]

Most GPs did not know how they could influence NICE' prescribing recommendations, and further added that they had never really thought about questioning the guidance provided by NICE.

I have never done it. I do not know, never questioned it! [P17]

However, most of them said they probably could find the information on Google if they ever needed it.

I do not know I would Google the site and look for where I could raise concerns. [P12]

I do not know, yeah. erm [pause] just look at… find online somewhere… a way of flagging up something. [P13]

Others reported that they find NICE to be visible through consultations and published guidelines.

I think, once they have published guidelines the are always very visible. […] And also, they do usually produce their draft guidelines for people to comment on, which I think, is a positive. So, there is an opportunity to get involved [P23]

Further, GPs reported that although they see the importance of challenging decisions made by NICE, they did not feel that they could make a difference as an individual:

They have not made it easier for their small guy to say… point these things out. [P6]

I am a little GP in your medical centre is the honest answer. Who am I to say, that they are wrong, is the honest truth. [P20]

GP7 said that this would be a job for their medicines management team:

It would be probably through our pharmacy medicines management team to say, if you know, "why isthis not in the formulary?" and then they could escalate it further up to NHS England and NICE, really. I do not think, and that is one of the things perhaps GPs do not really have an input into NICE, and I am sure you can email them, but it just does not happen, really. [P7]

Likewise, other GPs found that they would consult their local CCG or contact the local medicines management pharmacist if they had concerns or were unsure about recommendations from NICE.

I do raise a bit of my concerns to diabetic colleagues, you know, so when the consultant [inserted: later identified as being the local diabetes lead] comes here I do voice my concern to him [pause] he explains to me why certain things are done a certain way. [P4]

I would speak to the medicines management… up to the pharmacist upstairs and then we can take things further, higher up. [P16]

In summary, GPs found that NICE is not an accessible body however this shortcoming is overcome by easy access and good communication with local CCGs. Additionally, medicines management teams were also turned to for concerns or questions regarding NICE guidance.

4.3.2.4 Representation of primary care in the Guideline Development Groups

There was a mixed perception of whether primary care clinicians are well-represented on the NICE committees. Six GPs did not know, four GPs were unsure, and five GPs thought primary care was well-represented. However, these latter five sounded uncertain to the interviewer due to hesitance in their voice, and lack of knowledge of the structure of the committees.

Among those GPs who had more knowledge about the NICE committees and the decision-making process it was clearly expressed that they believed primary care healthcare professionals are not well-represented in the NICE Guideline Development Group.

I do not think they are very representative of the primary care in the real world [P5]

This was not only in regards to T2D but also in regards to other therapeutic areas.

… they can be criticised for being maybe unrealistic sometimes. [P6]

They found that the guidance sometimes seemed unrealistic about what is possible in primary care.

I do question sometimes what kind of primary care input has gone into that. [P19]

…there seems to still be a bit of a disparity perhaps between what they recommend and what is feasible in general practice. [P21]

The GPs suggested that NICE guidelines was driven by secondary care specialist who had little understanding of primary care practice

I think generally with NICE you find that there is maybe sort of weighting towards more secondary care people on the guideline review bodies. [P23]

I know several cases, in several guidance they are giving us where they have got no GPs on the panel, you know, the experts they are using are some tertiary care specialists that have no idea what life is like in general practice.[IP8]

GPs suggested that the gap between guidelines and practice could be closed by involving patients and a primary care healthcare professionals with varying experience with prescribing for patients with T2D

I think it would be helpful, to try and gage opinion in the community for those patients, for those clinicians who are on the shop floor basically, who are working either cold face seeing patients every day. [P7]

You also need non-specialist GPs and then if you are thinking broad we should be thinking about the podiatrist, we should think of dietitians, and we should definitely be thinking about nurses both the DSNs [inserted: Diabetes Specialist Nurses] and practice nurses. [P9]

I think it would be great to have a higher primary care experts […] in my area a lot of the diabetes care, and in some practices all of the diabetes care, is done by practice nurses and the nurse practitioners. [P23]

GPs identified a number of barriers to involvement of primary care healthcare professionals in the NICE committees. GP7 explained that the lack of engagement on the NICE committees from primary care healthcare professionals could be due to the lack of awareness about the consultations.

…because sometimes these processes kind of go under the radar of most GPs. [P7]

GP8 found that despite having an interest in diabetes the participant did not feel motivated to get involved in the NICE committee as it is not part of their salaried primary care role. The participant explains that any expense related to the participation would be from their own pocket e.g. GP locum cover, transport, hotel etc.

…and as much as I might be interested or develop a special interest or something, I certainly personally can't afford to spend thousands of pounds, just because I am interested. And that does not always seem to be taken account of. [P8]

Further, the GP compares this as opposed to secondary care healthcare professionals whose job description includes such involvement.

Secondary care, where part of their job is research and developing guidance and that is accounted for as part of their job, and they are very much encouraged to do that. [P8]

In summary, the GPs identified lack of encouragement for primary care clinicians to be involved in GDG and the high number of secondary care clinicians on the NICE committees as a reason for the gaps between clinical practice and guidance.

4.3.3 Antidiabetic medicines prescribing choices

In this section factors influencing GPs' T2D prescribing behaviours are described in respect to antidiabetic drug classes and their drug characteristics.

4.3.3.1 Glucose level targets

The GPs found that the treatment of patients with T2D is more target driven than it was in the past.

I think there is a lot more target… sort of a lot more target driven now than it used to be as well. [P19]

GPs reported that they were not sure about the evidence behind the chosen HbA1c targets in NG28 but they would use the NICE targets when they set goals for their patients.

I think they are good for goal setting. I know it is a bit arbitrary the HbA1c numbers which we have to follow. But it gives you a kind of yard stick to follow so that I completely use the NICE guideline. I would not feel equipped to do that myself [P10]

As consequence of flexible guidance NICE provides HbA1 targets, but they do not provide guidance on which drug classes to use to achieve these targets. In the example below it is demonstrated that GP9, as a GP with specialist interest in T2D, finds that the guidance does not provide any concrete recommendations on how to reach the recommended target levels and hence understand that non-specialist GPs may struggle with using the guidance for goal setting.

The 2015 guidance is certainly, gave really a big focus on individualising targets. Although not really giving us a lot of detail of what the numbers should look like, which I think, is not helpful particularly to… well it is not helpful to specialists, but particularly it is not helpful to non-specialists. [P9]

GPs were not certain about how often HbA1c levels needed to be monitored. They explained that the nurses were responsible for the monitoring and testing of the patients.

I am not quite sure, maybe six months' time or three months' time. [P16]

GPs were aware that blood glucose targets varied across national and international guidelines. They for instance mention treatment goals for older and frail as being tighter in the NICE prescribing guideline as compared to the American Diabetes Association-European Association for the Study of Diabetes (ADA-EADS) consensus report.

American Diabetes Association, they have quoted higher targets for frail elderly people and at the moment the NICE ones do not or apparently, they are going to? [P12]

NICE is out of kill compared to other international guidelines when it comes to that group [inserted: elderly population]. [P9]

In summary, the GPs were aware of the importance of monitoring the glycaemic targets when prescribing for patients with T2D and that there are variances in current national and international recommendations. However, there was little complexity in the descriptions beyond this.

4.3.3.2 Diet and lifestyle measures

Several GPs reported that the patients would receive structured education about their condition once they had been diagnosed. Depending on which geographical area the GPs were based on, the patients would receive education on diet and lifestyle from their practice nurses and/or through patient education programs such as Diabetes Education and Self Management for Ongoing and Newly Diagnosed (DESMOND) and Dose Adjustment for Normal Eating (DAFNE).

…we offer them to enrol on DESMOND educational program and there is also something called 'Wellbeing for life' which are specific to our local practice. [P6]

However, there was limited complexity beyond this. When the GPs were asked about how to get on these programmes, they had limited knowledge on the topic. As described further in section 4.3.6 patient education was often undertaken by nurses.

GP5 was the only GP who described diet and lifestyle interventions in more detail. GP5 stated that they had started treating the majority of patients with low carbohydrate diet. The emphasis on diet and lifestyle is for those who are interested in taking this route.

I have got a cohort of patients who are following a low carbohydrate diet. I have had several reversals. I mean, you call it 'putting diabetes into remission' really because you have to stick to the diet. [P5]

It was not clear from the interviews whether the patients would receive diet and lifestyle interventions *before* pharmacological treatment *or along with* pharmacological treatment.

I will always offer them the medicine straight away regardless. [P10]

That should be with first-line and with every line so every time were talking about intensifications. [P13]

In summary, although it was clear that GPs were aware about the importance of diet and lifestyle interventions it was not clear from the interviews how many patients were offered structured education. Further, it was not mentioned how they communicate with the local services which undertook the structured education training.

4.3.3.3 Preferred choice of antidiabetic drug classes

The GPs were asked about their preferred treatment choices at treatment initiation and first and second treatment intensification. Regardless of experiences with prescribing antidiabetic medicines the GPs were able to reflect on the changes in antidiabetic medicines prescribing practices. Antidiabetic drug classes ranging from thiazolidinediones, sulfonylurea, DPP4i, and insulin to glucagon-like peptide 1 receptor agonists (GLP-1RA) and sodium-glucose co-transporter 2 inhibitors (SGLT-2i) were reported as being as preferred second and third-line treatments depending on the context. In the following the GPs' reasons for choosing each drug class are presented in turn.

Most GPs reported that they would use metformin as first-line treatment unless it was contraindicated. They would push the dose to maximum dose or maximum tolerated dose, and if the HbA1c did not reach the target they would add a second drug.

> *…if they are hitting their target - great! If they are not, titrate the drug to their maximum dose or maximum tolerated dose, then if they are still not hitting the target discuss adding in something.* [P12]

> *…would work with metformin first and increase to the maximum tolerated dose, keeping an eye on the kidney function and monitoring the HbA1c and working on and modifying their lifestyle factors.* [P13]

Metformin was well-liked drug among GPs as the patients responds well to treatment, effective and has fewer side-effects as compared to other available treatments.

> *…basically it is a safe drug, we know a lot about it, you know, even the side-effects like the lactic acidosis it is astonishing […] it is usually well tolerated, there is the longer acting version, if it is not. And it has got that cardio protective, you know, kind of factor, that we are really interested in so that would be my first-line, go-to, generally."* [P8]

There was a general consensus among the GPs that the trend is going away from using sulfonylurea when treating patients with T2D.

> *I stopped using it as much in older adults.* [P12]

> *We used to use quite a lot initially gliclazide and all other sulfonylurea but we are not using sulfonylurea as much as we used to in the past.* [P14]

They explained that there are better alternatives available which are not associated with the risk of hypoglycaemia.

> *The hypo risk is high so glimepiride, glibenclamide all those medications. Gliclazide which is the one that is in our local CCG, I do not like*. [P4]

The GPs were hesitant using thiazolidinediones due to the side-effects profile of the drug classes.

I think, I feel like I am haunted by this thing with Rosiglitazone. And with the Glitazones in the past. And sort of there is always a sort of anxiety with the new drugs. I am aware that they are there, quite keen to use them but it is not really the cost it is more of the fact that they are new and we do not feel that they have not been around long enough. [P12]

Some of the glitazones that that we do not use anymore. Then there is still the kind of worry over the pioglitazones, when actually it is safer than we thought it was, and certainly there is not that affiliation with bladder cancer - things that we initially thought. That is starting to come through, although we still have to be careful, and I think that is the thing, it is not necessarily new drugs, but it is the kind of risk we know. [P8]

Further, it was described that once they had described potential side-effects to patients, they would rather be prescribed another antidiabetic treatment

When you talk to people about it, and you say to them, there is this tablet but it does have a low level risk of bladder cancer, actually many people do not want to take that. [P23]

GP6 believed that dipeptidyl peptidase-4 inhibitors (DPP-4i) and older insulins such as human insulin will be replaced by newer treatments.

Gliptins, I think have had their best day, I think. They are probably going to be superseded […] and obviously types of insulin that are used. [P6]

The GPs described newer treatments (GLP-1RA and SGLT-2i) as being efficient in bringing weight down and additionally also have cardiovascular benefits.

SGLT-2i acts on the kidney level, so you sort of glucose exchange and also helps with weight loss, it also has a cardio protection we will use <u>that!</u> So, it is all about trying different things for different people. [P4]

GP9 gave an example of an obese patient where the participant found it appropriate to use GLP-1RA instead of metformin as first-line treatment as per recommendations from NICE.

…here is talk of personalising care so can use that NICE guidance and still follow and still be with all the latest evidence. [P9]

However, it was not all GPs who agreed on the current positioning of GLP-1RA in the treatment algorithm. GPs rationalise why they tend to use the treatment sooner than indicated in NG28

I do tend to sort of use them sooner rather than later than what NICE would recommend. You know it is just that my idea is trying to get the patients diabetic control soon, better, quicker. [P4]

GLP-1 in particular is one which is I think is slightly inappropriately placed but again even then there is talk about using third-line… as a third-line option but it is quite restrictive in how to use BMI above 35 but then it comes up with a statement which you can use in people BMI below if they got severe comorbidities which can be improved. [P9]

A participant (GP4) finds that NICE recommendations are conservative and hence prescribe by the trial-and-error approach:

…ideally if you stick with NICE I think you have got to be a little bit more imaginative. And I think it is almost about trying different medications because then you get experience with the medications, so I like to try them. [P4]

GP6 gives an example of a patient where SGLT-2i works well but the patient experienced side-effects which the patient was willing to live with because other treatments had not worked.

He put up with lots of recurrent thrush, and even ended up having a circumcision, so that he could continue to [laughs] have this drug which is because he had not tolerated other drugs. [P6]

In summary, metformin was used at treatment initiation for the majority of the patients. However, it was not clear which antidiabetic medicines were being used as second and third-line treatment.

4.3.3.4 Insulin prescribing practices

The GPs described varying insulin prescribing practices.

I do not prescribe or initiate insulin. [P17]

I have to say, that I have never done it. [P20]

In some general practices they had nurses who could initiate insulin

We have a qualified diabetes nurse; she takes initiation of the insulin as well. [P15]

I would refer them to the diabetic specialist nurses. [P20]

Other GPs reported that they had joint in-practice clinics with consultants where they would initiate insulin.

We might be restricted from me initiating it but now that we have got this very joint arrangement where they come into our surgeries and we work together. [P5]

GPs who did not initiate insulin in their practice explained that they did not have any financial incentive to take on more responsibility

We do not receive any extra funding if we are the ones that initiate insulin. So it did not seem as if that was a worthwhile use of time. [P21]

We do not get funded for insulin initiation or get trained with it. So my nurses are not trained.[P3]

Further, the GPs report that they do not have the necessary training and knowledge to undertake insulin initiation.

… it was felt that in order to do that [initiate insulin] we would certainly need to do more learning, perhaps go on more courses etc with regards to that. [P21]

This is a confidence thing, but you need the training, and the backup, and the education, and we just have not got the resources to do that in primary care. [P8]

GPs who worked in general practices which *did not* initiate insulin were aware that other practices did initiate insulin.

I think we should be doing it. I know there is a lot of practices who are doing it. [P20]

We did talk as well about whether anybody here had an interest, among the partners, whether anyone here had an interest in starting to initiate insulin. [P21]

I would be happy to take over that prescribing, and I would be happy to refer for consideration of insulin. [P8]

However, the GPs identified a number of barriers to being able to initiate insulin in primary care such as lack of available appointments

These patients are going to need quite regular follow-up, are they not? It is the honest truth, and honest answer is, I probably have not got the capacity to slot them in because you can not just put someone on insulin and then not see them for two months or a month. [P20]

Among those GPs who *did* prescribe insulin they would prescribe it when other antidiabetic treatments had not worked for the patient

Failure of tablet management, really. [P10]

We put them on insulin after we have maximised all the medication, and if it is not working then they go on insulin. [P14]

If you have exhausted all your medications then the patient may need to go onto insulin at the end. [P17]

GP19 found that insulin is being initiated much earlier than it was in the past.

I think we are introducing insulin in a lot sooner than we used to. [P19]

GP4 does not share this view

I think we do not treat it acutely. You know, we just wait and wait, and wait, you know. I would rather they start with insulin sooner rather than later. [P4]

GP18 adds that GLP-1RA can be used as an alternative to prescribing insulin

I might use something like exenatide before I move to insulin. So, if it is failed everything else then I would give insulin. [P18]

Generally, the participants used insulin after trying two or three other drug classes or if they needed to bring down HbA1c.

Probably when I have tried three oral agents usually in combination but they might not have been tolerated. [P10]

I would probably say, if you know, we have tried generally a good four, you know, hypoglycaemic agents on maximum doses tolerated and then I would refer them for injectables. [P22]

and continues:

Whether it is insulin or you know something like [pause] I have forgot the class of drugs, you know…. The… what is the ones? [pause] The Byetta [pause] and I feel like I cannot remember... basically another injectable. [P22]

The decisions on which insulin to use was described to be driven by the local CCGs. GP12 for instance reported how the participant was encouraged to prescribe one type of insulin in one CCG and another type of insulin in the neighbour CCG.

…the diabetologist in [CCG name] seems to like us to use NovoMix 30, so nearly everybody who went onto insulin was on NovoMix 30 and in [CCG name] they follow more of the NICE stuff so they put people on a long-acting basal type insulin...[P12]

In summary, the use of insulin prescribing practices varied between the GPs. Some GPs were able to initiate insulin treatment while other only carried on with treatment initiated in secondary care. Further, there was described differences in the type of insulin used during treatment of patients with T2D.

4.3.4 Internal and external influences on antidiabetic prescribing choices

This section present findings on the GPs internal influences on their antidiabetic prescribing. This is followed by external influences which includes the use of NG28, CCG formularies and other secondary interpretative information resources. Further, it also elaborates on the influence of consultant and hospital prescribing.

4.3.4.1 Experience with prescribing antidiabetic medicines

When asked about the use of NG28 most of the GPs initially reported that they could not recall last time they used the guidance when making prescribing decisions and instead they showed the interviewer other guidelines on their desk or computer. As a consequence of using resources which are based on NICE instead of the NG28 itself, most of the GPs were not certain if their adapted prescribing practices were in accordance with the NICE prescribing guidelines.

I think, it is just becoming ingrained now, that you know, you start with metformin and then if the HbA1c does not improve you sort of move to one of the other ones. So, I think it does influence it because I would stick to that pattern with most people. [P23]

The use of metformin as first-line treatment was the only prescribing choice which was directly influenced by the recommendations in NG28

Well our standard is metformin. It is the cheapest, it is cheerful, it is well-tolerated, it works, so that is… tend to go down that route, metformin yeah. [P7]

GPs who identified themselves as experienced in antidiabetic prescribing would often see patients for whom standard treatment did not work.

I am often not really prescribing according to guideline because I am often seeing them as they have [inserted: other healthcare professionals in the practice] done the guideline treatment and its not been enough. [P10]

Experienced GPs who were confident in navigating through the available treatments reported that they more often would use newer treatment and their practices referred fewer patients to secondary care.

Because I am pretty experienced we have less patients that need, you know, decisions about type 2 management than maybe some places would have. [P6]

Prescribers were found to rely more on their own experience and develop head-held formularies as they became more established in practice. GPs for instance reported that they used their experiences in practice and knowledge from published clinical trials when choosing a drug rather than following guidelines.

*I suppose I just follow the guidelines and prescribe the ones that I am happy with and by prescribing you get experience with them and then you get more confident in their use.[*P5]

I tend to stick with trials rather than the guidance. So, you know, but broadly follow NICE guidance. But mainly about the glucose targets rather than the selection of agents. [P9]

It is probably not the guidance that much. It is more your experience with the tablets is the truth. [P20]

GP9 describes how it is easier to follow your own thinking when you have interest in the condition and have knowledge about the medicines on the prescribing guideline.

What I would say is part of the job which is challenging sometimes. Because a) if you are not interested in diabetes b) you are overwhelmed by the guidelines and confused by the medication. I am not either of those so that makes it easier for me because I find it interesting. I quite like talking to patients about those option because I find them interesting myself. [P9]

Additionally, GP10 who is a senior GP with specialist interest in diabetes said, that GPs are not experts in all fields of general medicine. For this reason, the participant would expect non-specialist GPs to seek guidance from diabetes experts when they had doubts about T2D related treatments. Similarly, the participant would seek guidance from other GPs when prescribing in a field which is not within their area of expertise.

I think, the great bit about NICE is you can not know everything and if you need to look something up, which you inevitably do, because you end up knowing some things quite well and other things less well. You just look on the clinical NICE summaries, that is what I use CKS [inserted: Clinical Knowledge Summaries] or the NICE website and then you have got evidence-based medicine to follow, sort of slightly thoughtlessly. [P10]

Contrary to the previous examples GP13 who is a registrar reported the increasing number of drug classes to be overwhelming. For this reason the participant finds that the variation in practice of GPs and lack of optimal treatment outcomes could be related to the lack of uniform guidance.

There is a lot of drugs, a lot of new drugs, things to remember, and there is no definite, you know, like with the hypertension, it is like we know exactly where we are going. With diabetes there is a lot more variable, a lot more patient factors. So, because it [inserted: NG28] is not as clear cut, it can be more variable in peoples practice and maybe that then affects control. [P13]

GP8, who has been qualified GP for four years described that the non-specific clinical guidelines made the participant feel insecure when treating patients with T2D. The participant decided to get a better understanding of the available drugs. As the participant gained confidence in prescribing for patients with T2D the non-specific guideline was no longer a challenge when prescribing for patients with T2D. As a result of the increased confidence in treating patients with T2D the participant has also started prescribing newer drugs which means the participant now refers fewer patients to secondary care.

…I think, the mentality of this is a 'secondary care condition', you know, put a drug or two in and then refer. Whereas now it is very much almost "just add this, add this, add this, add this", and I think as I have got more experienced and I have looked more into it. [P8]

In summary, the GPs only followed NG28 prescribing recommendations directly during treatment initiation with metformin. GPs with more expertise in antidiabetic prescribing were able to follow their head-held formularies at all stages of treatment. Less experienced antidiabetic medicines prescribers lacked guidance on how to choose between treatments after metformin.

4.3.4.2 NG28 prescribing recommendations

There was a mix report of the usefulness of the recommendations in NG28 due to its flexible nature

…there are number of options, you can always prescribe anything and you could not. [P9]

Some GPs were reluctant to describe the usefulness of the guidance

They do not seem unreasonable anything that I have looked at. […] The guidelines have always been sort of fairly as expected. [P10]

I would not say I entirely agree with them, but I would not say I completely disagree with them either. [P4]

However, it was not clear what the recommendation for second-line treatment after metformin actually is

There has been a bit of confusion as to what you are allowed to use second-line if you do not want to use gliclazide [pause] and that has been the changes that I've noticed. I am sure there are other changes but I am not really aware of them. [IP10]

Other GPs were critical of the recommendations in NG28. Their dissatisfaction was navigated by their specialist knowledge in diabetes.

I slide slightly from the guidance sometimes the guidance is a bit behind developments. [P6]

GPs found the recommended treatments were outdated when the guidance was published.

It was out of date when it was… actually, in my view, when it was published. [P9]

It is like gliclazide and all the rest of it is a bit… is going out of fashion a lot more. [P3]

Overall, the GPs were aware that the NG28 had been reviewed and updated since it was published in 2015. GP17 reported that updates or changes in the guidance from NICE is discussed at clinical meetings in the practice. For T2D the meeting would be led by the lead diabetes GP who would inform the other members of the practice about the changes in the guidance and how to implement these in practice.

…he will tell us, and then we look into it, and then we implement it. [P17]

One participant (GP3) did not read the actual guideline but made use of summaries of NG28

*I looked at three different people's summary table of them and I think the reality is I have probably looked at three different companies summary table*s. [P3]

GP21 reported to be cautious with referring to the NICE guidelines when making prescribing decisions as the recommendations are not always the same as those published by for instance GP Update and MB Medical.

"…there seems [hesitance in voice] to be a bit of disparity between how other organisation might manage it. So I think, there is a little bit more caution with regarding us referring to NICE guidance now" [P21]

The GPs had doubts about whether all relevant scientific evidence was considered during the consultations. It was especially the scientific evidence on newer drugs the GPs has concerns about.

…especially with diabetes there are so many products coming in you know, but NICE is not able to catch up with it. [P4]

Last time that they came out as a whole they were revised. I mean they are always sort of adding bits to it. Perhaps there was not enough emphasis on the of the newer drugs but I am thinking more particularly of the SGLT-2i, which I use quite a lot of. [P6]

Similarly, GP9 had concerns about NG28 as the participant found that it focuses on bringing down HbA1c and does not have enough emphasis on added benefits such as weight management and reduction of cardiovascular risk.

…my biggest objection is that it is too glucocentric. So, weight is not captured appropriately in that, and then particularly now with all the cardiovascular study data coming through, it looks like the whole costing model is slightly wrong. [P9]

A number of GPs reported that they found that The United Kingdom Prospective Diabetes Study (UKPDS) had too much influence on the prescribing guidance. However, GP9 was the only one who is specific about what the guidance lacks. The participant for instance found that there is not enough emphasis on treatment with weight loss benefit.

…not only is the evidence shaky […] *I mean patients' weight loss is not an important thing for them [inserted: NICE].* [P9]

The participant further added that an important study, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 diabetes Mellitus Patients (EMPA-REG OUTCOME), with proven cardiovascular outcomes was published two months before NG28 was produced. However, the committee did not do enough to consider the evidence and provide recommendations on the use of SGLT-2i.

The EMPA-REG outcome study came out in the October of 2015 and the guidance was published in December of 2015, so it was already out of date then. [P9]

GP7 agrees that the decision-makers have not given all clinical trials consideration. However the participant sympathises with decision makers position as a consultation is lengthy process and it takes time to put a committee together who can review the evidence to produce prescribing guidelines.

Although they are sometimes slow to pick up on what is actually going on in clinical practice. But that is understandable really, because if you are trying to put a guideline committee together, it is quite difficult. [P7]

In summary, there were varying beliefs about the usefulness of NG28. The GPs confidence to agree or disagree with the evidence was dependent on their expertise in antidiabetic prescribing.

4.3.4.3 Local formularies and other interpretive channels

GPs found that the treatment algorithm in NG28 (*see figure 1.3*) was too complex and instead of trying to familiarise themself with the guidance they would wait for other bodies to publish their guidance before implementing changes to their practice. Prescribing formularies provided by the CCGs were often mentioned as being used as their go-to guidelines. As the local formulary is based on the NICE recommendations the GPs still considered themselves to follow the NICE guidance.

Well we also have local guidelines, but they are based on the NICE guidelines so that seems to be the appropriate one to follow. [P23]

The GPs find that the local CCG guidance is more specific in terms of which drugs to prescribe as compared to the NICE guidance.

I find this harder and harder to keep up with the NICE guidelines and not only just for diabetes, we have intranet for [CCG name] that has for each like for gynaecology, for orthopaedic there is online guidance for this is, "what we would like you to do before you refer, this is what you need to try", and you kind of go for that first. [P5]

GPs also reported that the diabetes consultants in their local area would often prescribe medicines which were not on the NICE guidance yet. The reason for this being that local formularies are updated more frequently.

I think, the local diabetes consultants have come up with some guidelines and certain medications we have to use. We tend to stick to those guidelines and as long as we use those medications, they are quite happy with that. [P4]

They made use of means which they found to be good at synthesising information and presenting it in a way which was easier to understand and apply in practice than what was published by NICE.

…they will pull together all the guidelines from all the different guidelines and try and make out what we should actually be doing and summarise those. So, I tend to refer quite a lot to that as well. [P20]

… generally, just wait for the BMJ or for the Hot Topics. For the people to comment on the guidelines and then depending on what they say, is whether we use it. [P21]

Other mentioned examples of resources they would use included ADA-EADS consensus guidelines, Red Whale and GP update materials.

In summary, due to the lack of description of how to choose between treatments in NG28 secondary interpretative channels which were believed to be based on NICE guidance were used. The ease of understanding the guidance seemed more important than the evidence which had gone into the guidance.

4.3.4.4 Consultant and hospital prescribing

GLP-1RA and SGLT-2i were often associated with being "newer treatments". Most GPs were optimistic about the availability of new drugs as these have a potential to be used for patients whose treatment outcomes were unsatisfactory on standard treatment such as metformin. Newer treatments were appreciated for their ability to reduce glycaemic levels and improve cardiovascular outcomes.

I think the newer types of medications, the injections which are not insulin. They are called GLP-1RA? They are... seem to have added benefits of weight loss which is a massive issue in diabetic populations, so that could be one perhaps. [P7]

And:

So if they can get into treatment, which is very effective, very quick, and good at reducing their HbA1c, then that would be the best way forward really. [P7]

Antidiabetic medicines prescribed in secondary care were also reported to influence prescribing choices. Secondary care prescribers were perceived as "experts" and their opinions were respected by the GPs. Seeing secondary care consultants prescribe newer antidiabetic medicines gave the GPs confidence to adapt the same prescribing choices.

You do not tend to be the first adopter of a new drug I would always let my secondary care diabetes specialist use things for a while and then filter down to us. [P5]

I have seen a lot of that coming through from secondary care as well. So that is quite reassuring. Something, whether it is NICE guidance or not, I would be happy doing that. [P8]

GP5 reported that once they had seen their patients have positive outcomes from a new drugs initiated in secondary care it gave confidence to initiate the same drugs for patients in in primary care.

We only like to start using things in primary care that have been used in secondary care so you do not tend to be the first adopter of a new drug. I would always let my secondary care diabetes specialist use things for a while and then filter down to us. [P5]

GP8 whose confidence with prescribing was still developing described how the participant used referral letters to learn about secondary care consultants' prescribing preference. The GP used the referral letters to communicate with them which increased the participants confidence in prescribing antidiabetic medicines.

…every opportunity, every patient contact, for me, is an opportunity to learn or look at things where I am not sure, and certainly as a GP, you know, we get letters back from secondary care with thanks for referring, "you thought it was this, actually is that" or "yes, it was quite right, we are going to do this" [P8]

GP8 found that the communication with the secondary care consultants did not only help make better prescribing decisions, it also helped the GPr prepare the patients about what to expect once they had been referred to secondary care.

…you can sort of predict and work out what your management plans are going to be, and also to inform patients, you know, "I am going to refer you, they are most likely going to start this or do this" so they can get their head around it. [P8]

Similar to GP8' experience GP4 talks about how the complexity of the NG28 has made them rely on consultants. The participant describes that they were able to adapt practices shared by the consultants in their own practice:

I think, sometimes it is like the NICE guidelines it is too overpopulated. If you look at that the matrix it is mind boggling, it is confusing. So you just do not know what you exactly need to do. I basically liaise with my consultants and that is how I have developed a lot of my knowledge on it. [P4]

GP10 reported that they started prescribing Exenatide, which is a GLP-1RA, after the participant had seen it initiated by other healthcare professionals with good weight loss outcomes. However, the participant was not sure what the current NICE guidance was on the use of GLP-1RA.

I do not know where the whole exenatide and injectable ones come in and that is another one that I have seen quite a good weight loss with and that is obviously helpful. So, I think they might be in the guidelines now as part of triple therapy. [P10]

GP20 had been motivated to change prescribing practices by observing the way in which secondary care prescribers prescribed medicines. The participant described how that they would be letting the patients down if they did not improve their knowledge and skills to be able to prescribe newer drugs such as GLP-1RA.

I thought I was doing my patients a disservice if I did not provide that. A lot of the patients, I saw letters coming back from secondary care who were prescribing it [inserted: Byetta] before the insulin and I thought "well to be honest, why can not I do that?" rather than sending them awaiting six months to see a diabetologist to get the same thing really. [P20]

Seeing a new treatment used by secondary care consultants gave it acceptability and the GPs seemed to be less critical of their recommendations. Further, from the two examples above it is notable, that GLP-1RA were often referred to as "the injection which is not insulin" and "injectable ones" by the GPs.

Another example is GP6 who described how the participant started using SGLT-2i after seeing them prescribed by secondary care consultants although it was not on the NICE guidance at that time. The GP found their prescribing decision appropriate as these were supported by the local consultants and the GP expected the NICE guidance to be updated in due course.

I am talking to local consultants. That is not really out of step. It is just maybe moving on from that and obviously when you get new drugs it takes a while for them to be used and it consequently takes a little while for them to get into guidance as well. [P6]

GPs reported that it gave them a confidence boost when they felt confident enough to intensify treatment using a drug which they previously would refer the patient to secondary care for. GP8 for instance described how they prescribed a new drug using what they had learned from the consultants and when the GP discussed the treatment regimen with the local consultant afterwards, they appreciated that the GP made an effort and taken initiative to take on prescribing of newer drugs.

So, I think, just my understanding and pathophysiology knowledge and all the rest of it, I am a bit more aggressive, appropriately, with the appropriate patients of getting that down and managing and certainly pushing lifestyle changes as well. [P8]

In summary, GLP-1RA and SGLT-2i were associated with being the newer treatments in the antidiabetic treatment paradigm. The GPs adapted newer medicines prescribed by consultants and hospital prescribing as they were considered to be experts in diabetes.

4.3.5 Patient communication and treatment outcomes

In this section patient-related and health-care professional-related barriers to optimal treatment outcomes are described.

4.3.5.1 Views of patients' agendas and behaviours

In general, there was an initial push back against the idea of poor treatment outcomes among patients. Initially, most of the GPs were dismissive of this notion and argued that they were achieving their Quality and Outcomes Framework (QOF) targets.

I would dispute that because I mean obviously my [pause] very proud of our patient record. We hit QOF targets every year. [P6]

However, during the interviews the GPs acknowledged that it was not all patients who were well controlled on their current treatment regimens.

I think, we have got patients here that are very well controlled, and I think we have got patients whose control is frankly abysmal despite best effort. [P18]

The GPs identified barriers to treatment outcomes related to healthcare professionals and patients.

GP13 found that there is not enough emphasis on diet and lifestyle interventions in primary care.

I think maybe as GPs we want things medicalised the lifestyle modification is forgotten about or not mentioned enough, and I think we should take every opportunity, we should be reiterating that.[P13]

Delay in treatment intensification was found to be a major barrier to achieving good treatment outcomes. GP19 described how nurses are more lenient with the patients and let them decide the pace instead of setting reasonable treatment targets.

…often we [inserted: general practitioners] tend to be a little bit stricter than the nurses as well. In terms of you know, less likely to collude with the patients. [P19]

Other GPs added that even with the best efforts it can take as long as months or years before appropriate treatment targets are achieved.

I will do everything every three months but actually by the time you have got someone titrated up, that can actually… Could be in a couple of years, if we are not careful. [P18]

Sometimes the patients are found to have other priorities and unable to focus on their condition. GP4 gives an example of the consequences of letting the patients decide on the pace of the treatment.

We are late insulin starters as you are probably aware. North East has the highest insulin numbers for lower limb amputations due to diabetes and I think one of the reasons is we start insulin way too late. I think, we do not treat it acutely. [P4]

The GPs gave several patient-related explanations for why patients did not achieve their treatment targets. The most commonly mentioned reason was belief about patient behaviours such as adherence to prescribed therapy. GPs reported that they can check the patients' compliance from their prescribing software which would show them how often the patient was requesting each medicine.

Yeah so firstly we can when we look on our system. We can see how often they order it. […] We know sometimes people do order them but do not take them even though they order them and stockpile them I know that it is hard to find that out. [P23]

GPs reported that it is difficult to engage patients in diet and lifestyle measures and the medicines on their own cannot bring their Hb1Ac down to acceptable levels.

…a large portion of that is because they do not engage with lifestyle measures as whole heartedly as they perhaps could. [P10]

…I mean the thing that is going to make the biggest difference to people are diet and lifestyle. But people do not really want to change their diet so there is only so much medications can do. [P11]

Another GP adds:

We do use exercise on prescription as well, sort of thing, really to try and get them motivated, but again there is quite a lot of people, you can send them to as many things as you want but it will make no difference. [P20]

GP10 finds that patients for whom the diagnosis is an eye opener are more motivated and achieved better treatment outcomes

I would ball park one in ten are successful. But those people you see get such a shock with the diagnosis they actually go for it, and then they do it, and I think, it is worth letting those run with it.[P10]

Besides patient motivation the GPs also mentioned the patients' socio-economic status as a contributing factors to whether they achieve Hb1Ac targets

We are below the national target, okay. So in in [CCG name], in our local area, CCG and the neighbouring CCG, [CCG name], because of high levels of deprivation, poverty people could be much better controlled. [P7]

GP19 described that their patients have better treatment outcomes than patients in other general practices because they are well-educated

As a practice we are quite lucky because our patients are often quite educated and they also appreciate that. Whereas in other practices I think patients will be less so, and more inclined to do whatever they want. [P19]

In summary, the GPs were reluctant admitting that treatment could be optimised. A number of scenarios which led to clinical inertia due to patient and healthcare professional-related beliefs were described.

4.3.5.2 Shared-decision making

GP6 emphasised that it is rewarding to discuss the available treatment options with the patient rather than making a decision on their behalf and expect them to follow through with it.

> *So I think that is a really important part of it and rewarding, you know, as I say, that it is a bit of a puzzle and also dare say gives you little bit of kudos in the practice.* [P6]

As part of a personalised care approach the GPs also encouraged open dialogue. This means that they would encourage patients to talk about their medication preferences.

> *We really do work towards trying to make sure that they can tell us if they do not want to take a tablet, and also part of that is not starting them on any tablet if they do not want it*. [P23]

Overall, the GPs emphasised on the importance of involving patients in the decisions about their treatment and setting treatment goals which met the individuals' circumstances. Two examples are provided regarding GPs considerations when individualising treatment for elderly patients:

> *…then as patients are getting older, and living longer, we have to ask ourselves [pause] "what would intense control look like?" for let us say, a 90 years' old. Do we really need to have it the same as someone who is in their 40s? And I do not think that is being answered in research. And I, personally, kind of have that conversation with them, have that discussion really about how good treatment <u>they</u> want.* [P7]

> *I think, providing you have got a reasonable HbA1c, bearing in mind that life expectancy is very short, and it is all about how long you live with the disease developing complications, so you have got to really think about the individual patient*. [P6]

They would for instance, try to achieve a tighter glycaemic control with a middle-aged patient as compared to an elderly.

> *I think that looking at the age of the patient looking at other comorbidities might influence when I did or did not add anything further.* [P18]

> *A lot of our patients are younger in the city centre. So for them I think controlling their risk factors is really important because they are going to be living for you know 30-40-50 years*. [P3]

The GPs reported that some patient would want the GP to decide on treatment. However, as a part of shared decision-making they would still provide the patient with the available choices.

> *… when patient say, "no, you tell me doctor -you know better than me!" I always say, "this is my answer but that is based on <u>my own</u> preferences and values, they are not the same as yours, I suspect? I really want you to chip in if you can". Some do. Some do not.* [P9]

In general, they would listen to patients' request towards not being prescribed certain formulations. GP6 for instance had a patient who did not want to be prescribed insulin due to the fear of the potential side-effects of insulin.

She did not want to go onto insulin erm err so you [pause] she had very compelling reasons why she did not want to have insulin so we would explore those reasons, why you know, and the thought of putting more weight on, and having to do more monitoring was too much for her at the moment. [P6]

Contrary to GP6' experience GP4 gave an example of a patient who was not keen on swallowing tablets and for this reason insulin was offered as an injectable therapy.

I have had a patient who had a HbA1c of 115 who did not want to take tablets. I discussed insulin. She was happy with insulin. [P4]

GP4 further added that they intends to formulate a treatment plan which disrupts the patients' life as little as possible:

…it is basically trying to formulate my own plan, which I think, would benefit the patients. Something with the least follow-ups ,you know, which would benefit the patients. I do not want to keep changing medicine every time, I want patients to have as normal life as possible" [P4]

GPs mentioned that patients' adherence to the treatment regimen is a major issue which can be avoided by listening to the patients' reasons for not wanting a certain treatment:

If we just threw tablets at people because we feel that for our local figures we have to improve their HbA1c, then patients would not take them and they will just stockpile them, and that is a waste for everyone ones time and money. [P23]

It was emphasised that patients' motivation and patients' engagement were important factors to consider when choosing a treatment for the patients.

Giving them the responsibility back, that saying that, "yes, <u>you</u> need to look into these aspects, and then only the medication and the symptoms can be brought under control". [P16]

We are not in a place where we have personalised medicine, so I think capturing patients' preferences and values help shape what the right treatment or the need to treat should be there. At the end of the day the patient should take it. [P9]

In summary, the GPs believed that better treatment outcomes could be achieved by involving the patients in the treatment decisions. However, they found that the patients had varying interest in being part of this process. The GPs did not specify what they would do to change patients' belief or perceptions to engage them in the shared decision-making process.

4.3.5.3 Lack of guidance and training in use newer antidiabetic drug classes

The GPs found that they lacked training and guidance in how to use newer antidiabetic medicines. Their concerns were mainly associated with understanding and differentiating between clinical trial outcomes.

A bit more clarification about the new indications of the SGLT-2i is quite a big one because so many recent studies would suggest that there are certain ones that are good for people that have got cardiovascular disease but yet other studies have shown that perhaps they give an increased risk of foot problems. It is quite tricky to decide when to, and which one to use, and at the moment that is not really mentioned in any of the guidelines [P23]

I think the newer types of medications. The injections which are not insulin. They are called GLP-1RA? They seem to have added benefits of weight loss, which is a massive issue in diabetic populations, so that could be one perhaps. [P7]

GPs were holding back on the use of newer treatments despite that they find the drugs have more clinical benefits as compared to older medicines due to concerns about the cost of the medicines.

…and also, because they are quite an expensive drug compared to the old-fashioned drugs. Although I would happily use them, I would consider cost, but it would be prohibited for me to start. It would be nice for that to be a little bit more backed up in the guidelines. [P23]

I think, the cost needs to be renegotiated perhaps, looked at again. The cost-effectiveness and also the other group of medications called SGLT-2i, which are the ones where you urinate it out the glucose. [P7]

GPs found that it had become more challenging to choose between treatments as more evidence has become available which they have to take under consideration when making a prescribing decision

First of all they are getting more and more new drugs and then after that once they have been around for a while we start to hear more about them the risks and new side-effects that were not known before so it all just gets more complex once things are here, what their license are, you know. [P12]

We have more information about those different drugs about the benefits and the risks of them. [P23]

GP13 who was a registrar for instance described the changes in available treatments as compared to what the participant had learned during medical training:

I think, when I was in sort of in medical school and early on in my years it was more metformin than sulfonylurea and gliclazide straight away whereas as now, it is a bit different from that. I have seen more of the different medications being used more widely. [P13]

GPs who had more expertise in antidiabetic prescribing

So the biggest change over the past recent years is the number of glucose lowering agent you know there is quite, there is a large number of them. [P9]

… when I was first doing general practice it seemed to be just metformin and sulfonylurea and insulin and since then you have had DDP-4i and then the SGLT-2i and GLP-1RA and [pause] I do not know when glitazone came through. [P12]

The biggest thing has been the increasing number of different kinds of tablets that we are able to use now. When I first started it was really sort of a very limited number and now there is more options. [P23]

GPs generally agreed that it was important to consider switching patients when newer and better drugs became available. As an example a number of GPs with expertise in antidiabetic prescribing reported that they on their own initiative had switched their patients from the once-daily dose of Victoza to a newly available treatment, once-weekly dose of Ozempic, because it is more potent in terms of better glucose lowering effect and weight reducing benefits.

I want greater efficacy for the same price. [P9]

I do think, we also have responsibility to stop drugs when they do not work. I think we do not do enough of that. I think, it is really important that especially, well with any drug, but especially with the expensive ones if we have patients on those medications and we will review them their HbA1c is not improving we need to stop them. [P23]

Another change in the treatment paradigm is the availability of GLP-1RA as an alternative to insulin

…there is also more options with injectable treatments because when I started, GLP-1RA were not around. [P23]

In summary, the GPs found that they may not be using all available antidiabetic treatments to their full potential due to the lack of uniform evidence on the benefits.

4.3.6 Health system and practice influences on antidiabetic prescribing choices

This section describes the roles and responsibilties of primary care healthcare professionals and the changes in the delivery of care, respectively.

4.3.6.1 Roles and responsibilities of primary care healthcare professionals

4.3.6.2 Role of the General Practitioners

Overall when the GPs were asked which role *they* play in treating patients with T2D they initially described the process of care rather than their own roles. The GPs said that they were the first point of contact when patients presented with an illness in general practice.

…we book them to see our diabetic nurse, which is [name], otherwise if we suspect if patient is not diabetic then obviously as a GP we screen them for diabetes and once we know that it is a diabetic then again we book a double appointment with [name] for counselling for diabetes and for educations and to start medications. [P17]

I think in this practice we do have much more of just purely prescribing. Our nurses do the annual reviews, they do the recalls if any medications have been changed. [P19]

…we would generally speak and book them in with the doctor to get the diagnosis and then for at least half an hour with the nurse. Our nurses do not prescribe, our practice nurses, so the GP would prescribe generally speaking. They [inserted: the patients] get three months of grace for lifestyle and things and then we would introduce medication at that stage. [P19]

I will initiate metformin but then they get booked in for usually an hour long appointment with the nurse or a nurse practitioner who will go through everything in much more detail, do all the relevant diabetes checks and then arrange their follow-ups in three months' time where they will recheck their HbA1c. So management in this practice is very much nurse or nurse practitioner- led rather than GP-led. [P21]

The involvement of GPs and nurses also means that the general practice had their own delegation of who takes charge of which area of treatment. When the question regarding *their role in treatment* was repeated it was said that they were equipped to undertake all aspects of care.

We are probably equipped to do everything. [P10]

I think the GPs role specifically I think it is about diagnosis and getting them to the appropriate person for further management or initiating management if needs be. [P21]

We tend to be first port of call. We are the people who are monitoring things even if people are being seen by… specialist often calls for the GP for the rest of the drug monitoring, checking for side-effects, checking for compliance, checking how ,like I mentioned before, the holistic side of things. How are patients coping? They have been given X, Y and Z medication by specialist but how is that affecting them? Are they managing? [P13]

…at our practice our role is more in diagnosis and then reviewing them when something goes wrong, I guess. [P11]

GP13 was the only one, who identified the involvement of multiple healthcare professionals as an issue when providing care. The participant found that the patient suffered as there was no clear communication between the healthcare professionals within the practice about what has been done and what needed to be done.

We have diabetic nurses, we have practice nurses, we have GPs and sometimes it is almost if your using if too many people are involved then it is kind of like who is taking leadership of the condition, of the role. […] I think, sometimes GPs will then, may assume that things will be done by diabetic nurses or by practice nurses […] because it is not as clear cut, it can be more variable in peoples practice and maybe that then effects control. [P13]

We have a qualified diabetes nurse she takes initiation of the insulin as well. She starts them, she follow-up on them. That is our call. We are very minimally involved to be honest. [P15]

In summary, the GPs considered themselves to be the first point of contact when patients were treated in primary care. However, most GPs struggled to differentiate between their own role and other healthcare professionals' roles in the management of adults with T2D.

4.3.6.3 Role of the nurses

The nurses were described to play an important role in supporting the GPs so they could focus on diagnosing and prescribing for patients. Having a good nurse was described as an advantage in clinical practice as it takes some of the responsibility off the GPs.

Most of the time. nowadays diabetes is a nurse-led clinic most of the time. If nurses have problem they come to us but our nurse is good. [P15]

We are lucky to have our specialist diabetic nurse here which came only here six months ago. [P17]

The nurses could for instance educate patients about their newly diagnosed condition, titrate the prescribed medicine and conduct annual reviews.

Diabetic nurse she does all the education, she does all the basics she give them leaflet, everything. [P15]

They are very experienced. They might say okay "I have talked to somebody about the potential side-effects of metformin and do you think this prescription is appropriate?". […] We just organise a prescription. [P18]

The skills of the nurses were described to vary both within the general practice but also across general practices: an experienced prescribing nurse could for instance undertake the prescribing aspect of the appointment with patients. An experienced non-prescribing nurse could prompt the GP about which medicine they would like prescribed for the patient, and they would fill and sign the prescription accordingly. In case of more complex cases the patient could be booked in for an appointment with the GP after seeing the nurse. However, some practices had *very* experienced nurses who were also trained to treat complex patients.

…as I mentioned earlier like it is not that quite commonly, I receive patients. Like new diagnosis, like usually it is dealt with by our diabetic specialist nurse. She does a good job. [P16]

… well, probably if we had prescribing nurses, we probably could use them a bit more, our concern is that the nurses are a little bit twitchy about prescribing things. That is when you are initiating things. However when doses are needed to be changed some of our experienced nurses will knock on the door [knocks on table] and send us a task, and they will say: "I think this woman' metformin needs to be increased" or "her gliclazide needs to be increased" but the prescribing is mainly the GP. [P20]

However, GPs found that it was hard to keep good nurses in their practice. They explained that once the nurses had a certain level of expertise they tend to move onto secondary care, where they can keep developing their skills. In general practice, that means that the GPs either would no longer have a diabetes nurse to support them or they would have to train another nurse.

We lost one recently. She was poached by the hospital trust because she was so good and so you know it left us having to find someone else and train them up. [P6]

In summary, the role of nurses has been described to be variable. Most nurses would support GPs by being responsible for patient education in diet and lifestyle interventions as well as annual reviews while others also are involved in the pharmacological treatment of patients.

4.3.6.4 Role of practice pharmacists

Only four GPs directly mentioned having a practice pharmacist at the practice. The practice pharmacists varying presence in primary care and was mostly mentioned in terms of cost serving measures initiated by the CCGs:

We have got a practice pharmacist that comes in once a week and whether there is anything worrying or any massive overspends or very expensive new drug use, she will flag that up. [P8]

We have a pharmacist coming from the CCG. [P14]

Well, whenever we come to prescribe it [inserted: medicines], the prices come up so that would be the first place I would look at. The BNF gives an idea [inserted: of the price of the medicine] but if it was something kind of slightly unusual, then I would speak to the CCG pharmacist and ask her. [P19]

Our practice pharmacist once a year where they talk about sort of where we are in relation to other people. [P23]

Unlike their discussion of the nurse's role, the GPs were not able to clearly and confidently articulate their understanding of the role of the pharmacists.

In [city name] there is a clinical pharmacist who can talk about it and just make them aware of the diagnosis, those kind of things, initiate some treatment those kind of things as well but it has to be a clinician - so nurse, pharmacist or GP. […] He cannot actually prescribe. […] I think we have got to sign it off. [P22]

We do not stop things, but I think generally we are all getting better at stopping. I think, pharmacists can play a role. A little bit. We have a new medicine service around here, where if we give a new tablet the pharmacist will also counsel the patient and will also help follow up the patient, counsel… and I think they should, you know, they [community pharmacists] can feedback to us if either it is not being taken or they are having side-effects. [P23]

One GP, GP21, emphasised that they would not be influenced to change prescribing behaviour if the recommendation to change a medicine to a cheaper generic medicine came from a community pharmacist as compared to when it came from the CCG pharmacist. In the participants view the recommendation from a community pharmacist could be biased by financial gains for the pharmacy.

I think that, well the pharmacist who work in pharmacies and are not there to perhaps stick to guidelines or do what the CCG is… perhaps even… they are not necessarily there to convey the best evidence base… they have got an interest as an independent business to a certain extent. [P21]

In summary, the role of pharmacists was not very clear. The GPs realised that practice pharmacists were involved in different aspects of care in primary care but their role was not clear or well-defined.

4.3.6.5 Changes in the delivery of care

GPs found that an increased number of patients were being treated in primary care and subsequently less patient are referred for outpatient care in secondary care.

We are managing it and most people will not see secondary care unless things are deteriorating or were not managing it well. [P4]

Most of them never even enter secondary care. [P20]

I think very few type 2 diabetics need to go to secondary care. [P5]

Most of diabetes now can be managed in the community. [P7]

Diabetes which is becoming more and more primary care issue. [P23]

There was a general consensus among the GPs that primary care had moved away from having a generalist role towards having specialists within therapeutic areas. This change has been driven by financial incentives.

We get different level of payment depending on what percent of patients we care for in like primary care alone. And at our practice because I have maybe had a bit of extra experience with diabetes. […] I think, we manage ninety-six of all our diabetic patients here. [P23]

The growing number of available treatments were not found to ease the process of choosing an appropriate drug. As a result of the increased burden on the GPs they found they had to adapt and learn new skills and roles.

I have seen that we are managing a lot more in primary care now, and we are initiating a lot more drugs in primary care and there is a lot more drugs and whole classes of drugs available that were not available before. [P8]

You have got a chance to break that clinical inertia which is going on rather than referring them on to someone else. Because it [inserted: initiating injectables] is easier and it is safer, it requires less monitoring by primary care, but it is a great way to introduce injectable therapy to people. [P9]

We only refer very select few patients for the hospital so we have had to up our skills and training. [P23]

However, it is not all GPs who agree with the increased responsibilities

I am not thrilled about it because we are overwhelmed already, but I think, we are going to see the management and the initiation of the injectables, not necessarily insulin, but you know, especially if we get them [inserted: GLP-1RA] once weekly ones. That would become "get your practice nurse to do it" I do not think that is going to be a trait up to the hospital and the cost that goes with that. [P5]

In summary, there has been a shift in care between primary and secondary care. T2D is increasingly considered a primary condition however not all GPs agrees on the increased responsibility they have been given.

4.3.7 Cost

This section presents influence of cost on antidiabetic medicines prescribing in clinical practice.

4.3.7.1 Monitoring of expenditure on medicines

GPs said they were nudged about the prices of the chosen medicine when entering the name of the drug in their computerised prescribing systems. When asked if this influenced their prescribing decisions they said that it did not influence them to choose a medicines from another drug class but it would influence them to choose cheaper alternatives. GP18 for instance described how the prescribing software would influence them to prescribe cost-effectively

I would look and think, "oh it is more cost-effective for me to prescribe two tablets of 250 [inserted: mg] than one tablet of 500 [inserted: mg]" and I would do that. [P18]

GP20 explained how the participant for instance would not prescribe a liquid formulation of a drug where the tablet formulation of the drug is much cheaper. Here the participant explains that the decision would also encounter what the CCG would think of the prescribing decision

If someone asks for say, for liquid co-codamol I would hold my hand up and say: "yes, I will not prescribe that because you can get co-codamol tablets and I know that the CCG will want to know why I have prescribed that [inserted: liquid co-codamol]." So, cost definitely influence what I prescribe. [P20]

Most GPs said that their prescribing expenditure was monitored by the local CCG, and their practice' performance would be compared with other similar practices in their local area. GP5 for instance described that being compared with other practices in the local area would increase the pressure on the GPs to be cost-conscious

I think, you feel more pressure in that environment than you do looking at your QOF figures. [P5]

Further, GP6 reported that interest of the local CCG is not always the same as that for the clinicians. The local consultants for instance encouraged them to use a more expensive GLP-1RA than recommended in local CCG formulary.

I have also learnt from the consultants. I was prescribing the cheapest GLP-1RA and they were not really that brilliant at doing what they are supposed to on the tin, you know, and they have been trying, rather than just abandoning GLP-1RA, they have started getting me to prescribe, the maybe some slightly more expensive ones.." […] …they have been influencing me to spend more actually, but where, whereas I think the CCG would have liked me to be spending less. [P6]

GP5 reported to offer an increasing number of patients support to start on a low carb diet. The GP recognises that this measure should also contribute to bringing the overall medicine expenditure down.

I am really hopeful that my prescribing cost will come down more than everyone else is on the lifestyle. [P5]

4.3.7.2 Cost versus clinical benefits of treatment

The cost of medicines was perceived to be secondary to clinical effectiveness and safety. GP3 questions whether it really is a GPs job to consider the cost of medicines. The participant finds that it serves the patients better when prescribing choices are based experience rather than being driven by the cost of the treatment.

Is it my job to look at the cost of things? It is my job to be responsible but I am not searching out the cost going "I can prescribe you "a" or let me find one to pick the cheapest, it is actually this one, seems to be tolerated well and people take this one well, so I am going to prescribe you this one" [P3]

The GPs had instead adopted simple cost-reducing measures such as prescribing older treatment before newer treatments.

…I do not see any reason to put somebody on some fancy new your singing and dancing medication that you have not tried simple things that are proven over time to be effective. [P21]

GP8 would rather start with prescribing cheaper drugs such as standard-release metformin followed by the extended-release metformin which is more costly.

I m going to go onto the cheapest one first. The same with metformin. We always try normal metformin because it is cheap as chips and then if does not suit, we will, the you know, the modified release. [P8]

Similar example was given by G5

I like to prescribe cost-effectively and that is why I know metformin is cheap. It is got good outcome data, brings peoples HbA1c down, but you know you have got things like alogliptin that is £30 a month that does hardly anything, feels too expensive. But then, canagliflozin, similar level of cost but actually does seem to work far better. [P5]

The GPs believed that they contribute towards maximising the "value for money" by only prescribing expensive drugs for patients who were going to benefit from expensive treatment. They for instance would not typically prescribe an expensive drug for an elderly patient who had a short prospective life expectancy or patients who they suspected to be non-adherent to previous treatment regimens.

I was going to have a think really, I mean, I think considerations whether the patients going to benefit from that expense of drug. [P6]

It was a general perception that it was justifiable to spend more on treating patients with complex disease

I would be happy to prescribe it, even knowing it is more expensive because the hope would be that it would prevent complications. [P23]

GP7 was quite happy to ration newer medicines as the participant fings that newer drugs often are costly. The participant suggested that clinicians should be able to prescribe these expensive drugs as a private prescription for their patients if the patient requested the drug.

…we have to ration basically, and I am quite happy with that, rationing. To say: "this moment in time, we cannot prescribe a new drug because it is just not cost-effective for the NHS as a whole" […] but maybe give clinicians the option to prescribe it privately. If that is what the patient wants. [P7]

However, GP19 found that with the number of drugs available it was hardly necessary to prescribe the *really* expensive drugs to achieve good treatment outcomes.

I think at this age there is so many medications on the market that none of the ones that we would routinely use are extremely expensive. [P19]

GPs emphasised the importance of knowing when to stop or change treatment when it is not right for the patients as it is important for clinical reasons and to save on cost. GP6 gives an example how it the NHS can benefit from regular reviews of effectiveness of treatment

If a patient is poorly controlled on an expensive analogue insulin that was started six years ago or whatever, or when we had different priorities, then we should give it a go at offering the patient, and talk about maybe using a less expensive insulin, which may just achieve just as good control just for that patient. [P6]

4.3.7.3 Generic prescribing

Dipeptidyl peptidase-4 inhibitors (DDP-4i) were frequently mentioned as an example of a drug class where the CCG wanted to reduce cost by implement generic prescribing. The GPs described that the recommendations coming through from the CCG regarding which generic medicines to prescribe at times could feel like a "favourite of the month" rather than an evidence-based decision

That probably in three years' time they are going to say, "oh no, you can change it back now". Because it seems to happen quite a lot. [P3]

I mean gliptins, I think they really are expensive, you know, so those kinds of things they may be covered by CCG, you know, which one is a preferred one or which is the favourite of the month. [P22]

This has created resistance to change and frustration among the GPs as they find they already are under a lot of pressure. GP6 for instance reported that the local CCG wanted them to prescribe the cheaper version of alogliptin in order to save money.

We have been told to use alogliptin because it is cheaper than the other gliptins. It will not have anything to do with the efficacy because they are within the class, they are all very similar [P6]

They found that it did not always seem like the CCG had encountered other factors besides the price of the medicine. As a practice they had to counter other factors such a available appointments

It is costing more on nurse appointments to bring those people in to do dose titrating. [P3]

Further, GP3 and GP14 said that their CCGs would sometime intend to take some of the burden off from general practice by sending letters to the patients about the change in medication on their behalf.

If they [the CCG] want to change any treatment, like metformin changed to a drug called Sukkarto MR which is a little bit cheaper. So, he [inserted: CCG pharmacist] comes and he explains to all of us and then we agree. You have to sign some paper and then the CCG is sending letters to the patient from here [inserted: on behalf of the general practice] that these are the medication we are changing from this one. [P14]

GP3 did not find that this would decrease the burden on the general practice as the patients would request appointments to get a clarification of why their medicine had been changed.

That will create some work for us. Some one, two or three people will want to speak to us about that. Now if they cannot? They want to come in! That is appointments! [P3]

4.3.7.4 *Influences of performance indicators*

QOF targets were identified as being important as meeting these requirements ensured that the general practice gets paid for treating the patients.

The GPs found that QOF targets and NICE recommendations did not always go hand in hand. Most GPs for instance said they would tailor treatment for elderly patients as per NICE recommendations.

*I did not mention about recent NICE guidance was tailoring the treatment to the patient. In the past, we might have been target driven and we might have been getting patients who have their HbA1c levels thinking about elderly patients, frail patients who <u>really</u> their target should have been over the QOF target that we are aiming for. So now, we are sort of taking the foot of the gas for many patients. [*P6]

However, in practice this would mean that they would aim for higher Hb1Ac targets than indicated in the QOF scheme to qualify for payment

…you have got a 90 year [old] in a nursing home, you know, it is inappropriate to drive them down to the QOF targets that we have got. [P5]

I think providing you have got a reasonable HbA1c bearing in mind that life expectancy is very short and it is all about how long you live with the disease developing complications, so you have got to really think about the individual patient. [P6]

GP3 similarly said that incentive payments make it difficult to balance between treating patients for clinical reasons and financial reasons

You try and commit to people that obviously do need the care to come in but equally to function as a business you kind of go "oh I need to get some of these easy wins in" because we need to function as a business we need to get the revenue in the door otherwise we cannot pay staff. [P3]

Other GPs also talked about how the QOF targets can challenges one's clinical decisions making. GP4 described concerns regarding choosing appropriate drug to bring down Hb1Ac quickly and thereby qualify for the payment. In this example GP4 explains that although sulfonylurea may reduce the patients' HbA1c level quickly it is also likely to cause hypoglycaemia, and if the patient is not able to identify the red flags it can be life endangering.

Sulfonylurea is not my first choice in bringing their HbA1c down. Because I know that a lot of my colleagues will say that, you know, it is great for bringing their HbA1c down quickly so that you can get your QOF points and everything else, you know, but I know that is an easy way to do it but you are risking hypoglycaemia and unless you have a very thorough sort of you know explanation to the patient because they are probable you know if they have not experienced hypoglycaemia they will not know the seriousness of it and what it can cause and how to recognise it.[P4]

GP9 emphasises that you, as a GP, will always be held accountable for your clinical decision and for this reason it is important to base your decision on the provided guidelines.

> *Certainly, people who fund healthcare are responsible for funding in NHS England or CCGs. They are going to see the NICE guidance almost as the gospel so anybody going away from that there needs to be clearly explained why and then provide clear rationale behind that.* [P9]

4.3.8 Conceptual model of beliefs influencing antidiabetic prescribing practices in primary care

The interviewed GPs described beliefs which consciously or unconsciously influenced their prescribing decisions across the three levels of healthcare. Their reasons were often unpredictable and driven by interactions with the patients as well as policy and practice regulations. Figure 4.3 illustrates that GPs antidiabetic medicines prescribing practices were influenced by complex and multifactorial internal and external influences. C*haracteristics of antidiabetic medicines* (license, side-effect profile, proven clinical efficacy and price of treatment) were found to influence the prescribing recommendations provided by NICE as well as local strategies and incentives in CCGs. *Role of NICE in clinical practice* (using NICE guidance is learned behaviour, the theoretical role of NICE is well-regarded) further influenced the produced T2D guideline (currently NG28), local CCG formularies and other published sources. NICE was also found to influence the local strategies and incentives in CCGs. *Internal influences* (professional confidence, experience with antidiabetic medicines prescribing, perceived prescribing behaviour norms and medical training) influenced the GPs view of NICE and their prescribing recommendations. Moreover, it influenced their confidence to use the range of available antidiabetic medicines while considering patient communication and treatment outcomes, characteristics of antidiabetic medicines and regulations from NICE or CCGs.

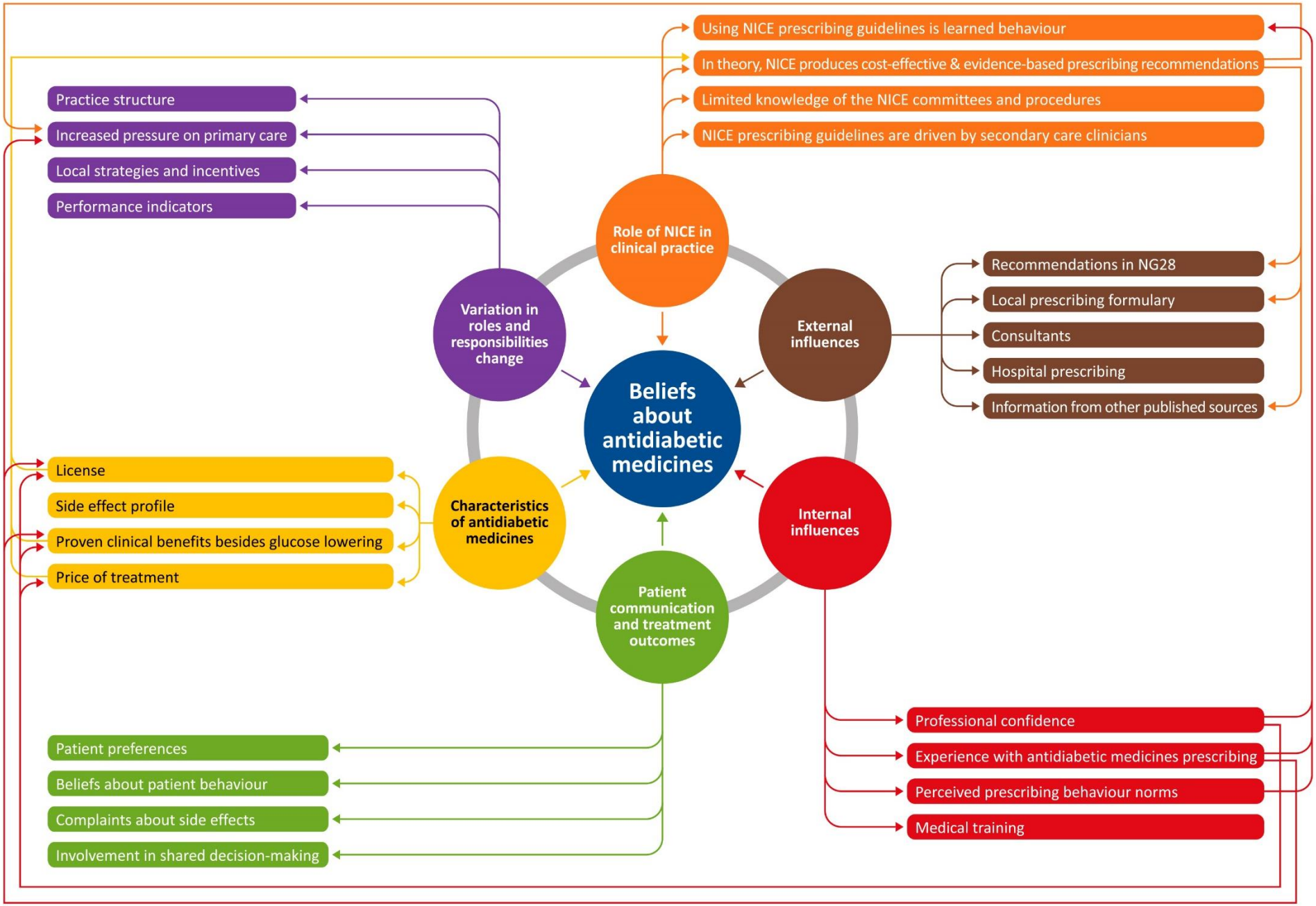


Figure 4.3 Conceptual framework describing key influences on general practitioners' antidiabetic medicines prescribing practices in primary care.

4.4 Summary of beliefs and behaviours influencing antidiabetic prescribing in primary care

This is to the researcher's knowledge the first documented study on GPs understanding of the role of NICE in clinical practice and beliefs about antidiabetic medicines prescribing in primary care in Northern England. Figure 4.3 illustrated the connectivity and overlap between the three levels of healthcare and the major influences on antidiabetic medicines prescribing in primary care. In the following section the findings from the qualitative study are summarised according to objectives and research questions as described in section 4.2.

1. What is the perceived value of NICE in clinical practice?

The GPs reported to trust the prescribing guidelines produced by NICE. They found that the recommendations published by NICE, in theory, ensures uniformity in healthcare provision. The GPs lacked knowledge about *who* is involved in the development of the NICE guidelines. GPs expressed concerns about the transparency of the selection process of members of the GDG. Further it was also questioned whether the decisions made by the NICE committees were driven by clinical experience or scientific evidence. The involvement of a high number of secondary care clinicians on the GDGs and their lack of understanding of primary care practices were identified as a potential reason for the gaps between clinical practice and guidelines. The GPs did not have any doubts that secondary care clinicians are experts in treating patients with diabetes. However, they wanted more primary care clinicians involved in the NICE committees so they could advocate recommendations which are adaptable in primary care setting.

2. How useful is NG28 when making prescribing decisions during day-to-day prescribing?

Prescribing for patients with T2D was not described as linear process. However, it was not described as being a chaotic process either. GPs experienced with prescribing for patients with T2D were found to have stronger opinions about the recommendations in NG28 than those who were less experienced with prescribing for patients with T2D. Overall, the GPs found that the NG28 was too vague to offer any valuable guidance for clinicians when choosing between available drugs classes. Some GPs found the guidance was outdated when it was first published in 2015. There was also varying views on whether the prescribing recommendations in NG28 was up-to-date with scientific evidence at the time of the interviews. Those GPs who were experienced in prescribing antidiabetic medicines often followed head-held-formularies as compared to other GPs who relied on the published guidance. For this reason less experienced T2D prescribers also found that they lacked guidance and training in how to use newer treatments such as SLGT-2 inhibitors and GLP-1RA.

Although the GPs may not be using the NICE guidance as their go-to guidance they did believe that it plays an important role to inform other guidelines such as local CCG formularies. Their clinical decisions were found to be influenced by availability of drug in their local prescribing guidelines and prescribing recommendations from the local consultants. Prescribing recommendations given by consultants were

especially valued by less experienced antidiabetic medicines prescribers. It appeared that less experienced GPs would only prescribe within their comfort zone. This meant most of them would be reluctant prescribing treatments which they were not familiar with. They reported that they would only prescribe insulin or newer drugs such as GLP-1RA and SGLT-2i when other options had been explored or as follow-on prescribing from another prescriber. The GPs also reported that were happy to follow recommendations from the consultants, once they have been applied in practice even before the NICE committee had reviewed the clinical trial evidence on a new drug. It was observed that the GPs did not express any critical appraisal of the recommendations provided by the consultants as compared to when they talked about guidance provided by NICE.

Overall, when the GPs described scenarios most of them did not mention any specific HbA1c targets. They explained that the recommendations for HbA1c targets keep changing and hence they would regularly need to look these up.

3. ***How do the GPs choose between antidiabetic medicines when treating patients with T2D?***

Firstly, it is important to emphasise that the number of years in GP practice was not found to equal more experience with prescribing for patients with T2D. The GPs explained that the variation in experience with prescribing for patients with T2D was due to their training in prescribing for a variety of conditions. GPs who had T2D a speciality area would therefore be more experienced in prescribing antidiabetic medicines. In this study it was for instance observed that GP8 who had three years of experience as registered GP had developed skills within diabetes as the participant did not able to deliver the quality of care which they expected of themselves. Likewise, GP6 had their own motivation for adapting a low carb diet and working with patients on diet and lifestyle measures. The participant was successful in bringing a larger number of patients into remission than other colleagues who did not use the same approach. GP9, who was also a CCG lead, found that due to involvement in local prescribing policies the participant for instance was more critical towards the recommendations in NG28.

The length of time in general practice did not seem to influence the GPs observations of the changes in prescribing practices. All GPs were aware that the landscape of antidiabetic medicines to treat T2D had changed. GPs who had been in practice for a long time experienced this through the availability of the number of new treatments over time. Younger GPs described that the landscape of treatment was more complex than it had been described in the books during their medical training.

Secondly, having knowledge about the increase in number of available treatments did not necessarily mean having confidence in using these. GPs who were experienced in the use of antidiabetic medicines were able to navigate the landscape of available treatments and choose an appropriate therapy based on their experience. GPs with less experience with prescribing antidiabetic medicines mostly described the use of older treatments. If the patient was not managed by the therapy, they would have to refer patients to more experienced prescribers who could escalate therapy. This could be experienced GPs or nurses within the practice, joint-clinics or outpatient care.

GPs believed that in order to get the best treatment outcomes it was important to get the patients involved in the treatment. Although it was not clear from the interviews how many GPS offered their patients structured education about the diet and lifestyle the present study confirmed that that GPs found it difficult to engage patients in their treatment plans. Further, the availability of patient education programmes varied across CCGs. Some GPs reported that their nurses would undertake the patient education whereas others sent their patients for structured patient education programmes such as DESMOND and DAFNE. Furthermore, the GPs also reported that they did not find many patients to be successful in getting their diabetes in remission with diet and lifestyle changes only. For this reason, they would often add treatments along with offering diet and lifestyle advice.

There is still a need to further investigate which drugs GPs are prescribing for their patients. The GPs described scenarios and situations where they would deviate from their regular prescribing approach. It was difficult to capture the stepwise approach in the qualitative phase due to the nature of interviews. Metformin was mentioned as GPs preferred first-line treatment for asymptomatic patients. However, they would prescribe alternative drugs for patients where metformin was contraindicated or not tolerated.

In general, the GPs reported that the trend is going away from prescribing sulfonylurea. This was explained by availability of newer and more effective drugs which did not have the side-effects profile such as sulfonylurea. Likewise, GPs were hesitant prescribing thiazolidinediones due to their history of adverse events. DDP-4i was often mentioned in relation to cost-effective prescribing and generic substitutions. The prescribing of insulin was described to vary in primary care as some GPs were able to initiate insulin while others had to refer the patients to secondary care. GLP-1RA and SGLT-2i were praised for their clinical benefits, however the use of these varied depending on the CCG and the local use of the drugs. The GPs reported a number of drug-related factors such as patients' characteristics (age and clinical condition), pharmacology, efficacy, safety, tolerability and cost to influence their prescribing decisions. Furthermore, the GPs also reported patients' preferences such as patient motivation, lifestyle and job to influence their drug choices.

The clinical management of patients was perceived to be a result of a mutual efforts from the clinicians in the practice and the clinical management of adults with T2D is undertaken by a multidisciplinary care team. The roles within these teams varies across practices. The availability of experienced healthcare professionals within the general practice determined which level of care the individual practice could provide their patients. The GPs also reported a number of cost-related factors which influenced their daily prescribing practices. On an individual level they reported that they have a responsibility to spend responsibly. This ethos was at times found to be challenged by external influences such as cost-reducing interventions from local CCGs and performance indicators such as QOF.

CHAPTER 5

Study 2: Cross-sectional survey on primary care clinician's antidiabetic prescribing practices in Northern England

5.1 Introduction

This chapter presents the second study (study 2) of the exploratory mixed-methods study. The chapter begins with a recap of findings from study 1. Then, it outlines the aims and objectives followed by findings from study 2. Finally, in the end, a reflective summary is presented.

5.1.1 Qualitative findings that informed the conduct of Study 2

The results presented in chapter 4 were derived from qualitative interviews (study 1). It was established that the interviewed general practitioner (GPs) value NICE however their use of NG28 was dependent of their belief about antidiabetic medicines. The GPs described varying use of antidiabetic drug classes which were influenced by local formularies, consultants and hospital prescribing. There was also observed differences in the insulin initiation practices as some GPs were able to initiate treatment within the practice while others had to refer for outpatient care. Through the interviews it was observed that the role of the GPs depends on the organisational structure of the general practice. Additionally, the GPs described that nurses were involved in the patient education and management of non-complex patients. These findings suggested that nurses, and in some practices also practice pharmacists, were involved in making prescribing choices for patients with type 2 diabetes (T2D). For this reason, it was observed that for an accurate portrayal of prescribing practices, it is important to explore the views of all involved primary care healthcare professionals. This study complements findings from study 1 by asking questions related to key findings.

5.1.2 Aims and objectives

The overall aim of study 2 was to characterise the prescribing practices of primary care clinicians. The objective of this study was to conduct a cross-sectional survey of general practices in North England. The aim was to investigate:

1. Which prescribing guidelines do primary care clinicians use during their day-to-day prescribing?
2. How do primary care clinicians manage adults with T2D?
   2.1 What is the preferred stepwise approach to antidiabetic medicines prescribing?
   2.2 Which criteria do they use to choose between antidiabetic drug classes?
   2.3 Who do they seek guidance on use of antidiabetic medicines from?
3. How common is insulin initiation in primary care?
4. Which cost factors were considered when making antidiabetic prescribing choices?

The findings from the survey are presented below. First data regarding the respondents' demographic characteristics are presented (section A and B). This is followed by results on the use of prescribing guidelines (section C) and clinical management of adults with T2D (section D). Last, results on the cost of antidiabetic medicines are presented (section E).

5.2 Findings

5.2.1 Characteristics of respondents

A total of 145 questionnaires were returned. Out of these, 80 responses were through the postal survey and 65 responses through online survey. Twenty responses were excluded before the analysis of data: Four responses were excluded as they had been returned blank and 16 responses were excluded because the clinicians worked outside the geographical area. Valid responses from 125 participants were included in the analysis. Table 5.1 shows the distribution of the valid responses. The majority of the responses were completed in round 1 (31%) and round 4 (37%).

Table 5.1 Distribution of postal and online responses (*n=125*)

	N	%
Postal	79	63
Online	*46*	37
	N	**%**
Initial postal survey *(round 1)*	*39*	31
Postal reminder 1 *(round 2)*	*27*	22
Postal reminder 2 *(round 3)*	*13*	10
Online survey *(round 4)*	*46*	37

Figure 5.1 depicts the areas in Northern England from which the survey responses were returned. At least one response was received from 47 (71%) Clinical Commissioning Groups (CCGs). Three or more responses were received from 15 CCGs (Bradford Districts CCG, East Riding of Yorkshire CCG, Liverpool CCG, Sheffield CCG, Vale of York CCG, Bradford City CCG, Darlington CCG, Doncaster CCG, South Tees CCG, Central Manchester CCG, Durham Dales Easington & Sedgefield CCG, Greater Huddersfield CCG, Tameside & Glossop CCG, Hartlepool and Stockton-on-Tees CCG, Newcastle & Gateshead CCG). The number of responses from each CCG (n=47) has been presented in appendix 20.

Figure 5.1 Geographical representativeness of respondent's local area according to Clinical Commissioning Groups as per December 2018. Map created with ONS®.

As presented on table 5.2, 46% of the respondents were GPs, 31% nurses and 16% pharmacists and 7% did not indicate their profession. The largest proportion of respondents (37%) were between 51- 60 years old, followed by 41-50 years old (32%). The majority of the clinicians had between 10 and 39 years of experience. Eighty percent of the clinicians had the authority to prescribe, 18% did not prescribe and 2% did not respond to this question.

Table 5.2 Demographics of respondents.

	N	%
Sex		
Female	73	58
Male	45	36
Prefer not say	7	6
Profession		
General practitioner	57	46
Nurse	39	31
Pharmacist	20	16
Not indicated	9	7
Age (years)		
<30	3	2
31-40	26	21
41-50	40	32
51-60	46	37
>60	7	6
Not indicated	3	2
Years since qualification		
0-4	4	3
5-9	4	3
10-14	11	9
15-19	15	12
20-29	36	29
30-39	34	27
40+	5	4
Not indicated	16	13
Prescribing status		
Yes	100	80
No	22	18
Not indicated	3	2

5.2.1..1 Healthcare professionals involved from primary care team

The respondents were asked which healthcare professionals in their general practice were involved in the care of patients with T2D. The responses (see table 5.3) indicate that the GPs were the most frequently involved clinicians (78%). This was followed by practice nurses (70%), practice pharmacists (26%) and diabetes specialist nurses (23%). Additionally, half of the respondents stated they had an in-practice diabetes care team (yes=49.6%, no=49.6%, unsure=0.8%).

Table 5.3 Healthcare professionals involved in the care of patients with type 2 diabetes mellitus, multiple choice.

	n	%
General practitioner	98	78%
Practice nurse	88	70%
Diabetes specialist nurse	29	23%
Pharmacist	33	26%

5.2.1.2 Multidisciplinary healthcare team across healthcare settings

The clinicians were asked who they would seek guidance from if they were in doubt of which antidiabetic medicine to prescribe for their patients. They were given the opportunity to choose multiple options

(figure 5.2). The four most frequently routes of seeking advice were contacting secondary care diabetes team and asking for advice (62%), asking an internal diabetes specialist nurse (54%), referring patients to a secondary care diabetes team (38%) and asking a general practitioner (30%). A Chi-Square test of independence indicated significant differences in the proportion of GPs versus other healthcare professionals who would seek guidance regarding which medication to choose from another GP, X^2 (1,N = 112) = 8.92, p = 0.03.

Figure 5.2 Internal and external clinicians which the respondents' would seek guidance from regarding prescribing (question 32, multiple choice).

The survey responses showed that participants frequently reported to seek help from the other healthcare professionals *when patients presented with specific or difficult problems (63%), uncertainty of the therapeutic needs of the patient (44.3%)* and *polypharmacy concerns* (34.7%). It was also noted that about one fourth of the respondents would consult other healthcare professionals about *patients presenting with adverse drug reactions (25.2%)* (figure 5.3).

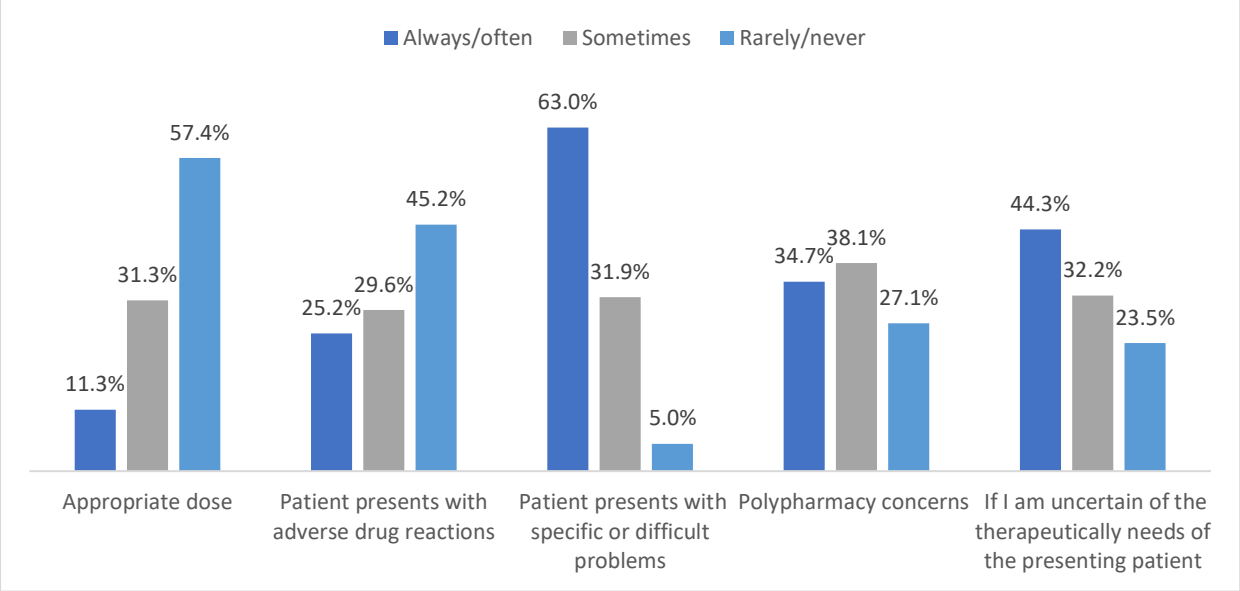


Figure 5.3 Reported reasons for seeking guidance from other healthcare professionals regarding appropriate dose, patient presents with adverse drug reactions, patient presents with specific or difficult problems (questions 33-37, multiple choice).

A Chi-Square test of independence indicated significant difference in the proportion of GPs versus other healthcare professionals who would seek guidance regarding *patient presents with adverse drug reactions*, X^2 (1,N = 106) = 8.85, p = 0.012 and *patient presents with specific or difficult problems*, X^2 (1,N = 110) = 8.41, p = 0.015.

5.2.2 Use of prescribing guidelines

The survey intended to investigate the clinicians' use of prescribing guidelines. Based on the findings from the qualitative study (study 1) the focus was on the use of NG28, ADA-EADS prescribing guidelines and the use of the local CCG formularies.

Table 5.4 shows that the majority of the clinicians (84.0%) felt confident regarding prescribing medicines for adults with T2D using the current guidance provided by NICE. However, there was a varying views of if NG28 was up-to-date with scientific evidence at the time of publication (*yes*=35%, *no*=26%, *unsure*=39%). A Chi-Square test of independence indicated significant differences in the proportion of GPs versus other healthcare professionals who found NG28 to be up-to-date with evidence at the time of publication in 2015, X^2 (1, N = 67) = 6.06, p = 0.014. Only 17.1% found NG28 to be up-to-date with scientific evidence at the time of the survey.

It was observed that in the past two weeks 18.5% had used NG28, 28.9%% had used ADA- EASD guidelines and 36.8% had used their local CCG formulary when prescribing for patients with T2D. A Chi-Square test of independence indicated significant difference in the proportion of GPs versus other healthcare professionals who had consulted the ADA-EADS consensus guidelines for prescribing purposes in the past two weeks, X^2 (1, N = 109) = 9.04, p = 0.03.

Table 5.4 Participants self-reported use of prescribing guidelines

Statements	*N*	Yes (%)	No (%)	Unsure (%)	General practitioners versus other healthcare professionals, *p*-value [a,b]
Do you feel confident prescribing medicines for adults with T2D based on current guidance provided by NICE?	125	105(84.0%)	11(8.8%)	9(7.2%)	0.801
In your opinion, was the NICE 2015 treatment guideline [NG28] up-to-date with evidence at the time of publication in 2015?	123	43(35%)	32(26.0%)	48(39.0%)	**0.014**
In your opinion, is the NICE 2015 treatment guideline [NG28] up-to-date with current evidence?	123	21(17.1%)	60(48.8%)	42(34.1%)	0.554
Have you consulted the NICE guideline [NG28] for prescribing purposes in the past two weeks?	124	23(18.5%)	100(80.7%)	1(0.8%)	0.391
Have you consulted the ADA-EADS consensus guidelines for prescribing purposes in the past two weeks?	121	35(28.9%)	82(67.8%)	4(3.3%)	**0.003**
Have you consulted the local CCG formulary for prescribing purposes in the past two weeks?	125	46(36.8%)	77(61.6%)	2(1.6%)	0.180

[a] p-value calculated through the Chi-square test.
[b] $p < 0.05$ considered statistically significant results.

As shown in table 5.5, 47.6% of the participants agreed or strongly agreed that the drugs recommended by NICE in the NG28 guideline were adequate to treat patients with T2D. Also, 46.7% of the respondents agreed or strongly agreed that NICE has taken longer to update the guidelines on management of adults with T2D compared to their local CCGs. When asked if NICE is effective in managing the budget for medicines and achieved the widest possible range of medicines from the available funds 41.0% of the respondents agreed or strongly agreed. A further 40.2% stayed undecided or neutral to this statement.

Table 5.5 Participants perception of the recommendations in NG28

Statements	*N*	Agree/ Strongly agree	Undecided /neutral	Disagree/ Strongly disagree
In your opinion, are the drugs recommended by NICE in the NG28 guideline adequate to treat patients with T2D?	124	59(47.6%)	35(28.2%)	30(24.2%)
In your opinion, has NICE taken longer to update the current guideline on management of adults with T2D compared to your local CCG?	120	56(46.7%)	49(40.8%)	15(12.5%)
NICE is effective in managing the budget for medicines and achieves the widest possible range of medicines from the available funds	122	50(41.0%)	49(40.2%)	23(18.8%)

Similar to the findings in the qualitative study, the respondents had mixed perception of whether they were given sufficient opportunity to make their concerns regarding prescribing recommendations known to NICE (figure 5.4).

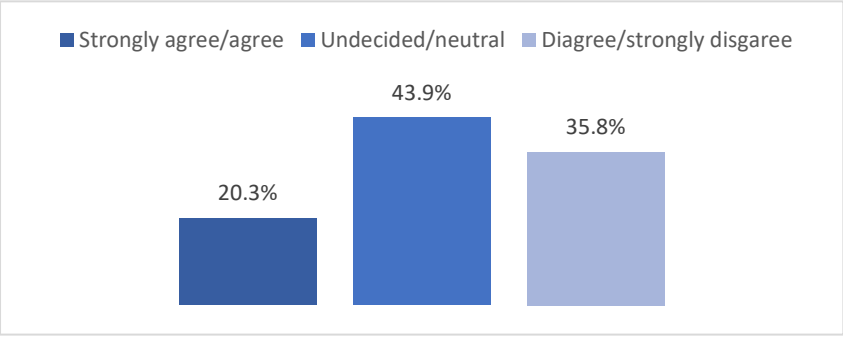


Figure 5.4 Participants' perception of opportunities for primary care healthcare professionals to make their concerns known to NICE (question 12).

Similar to the qualitative interviews, there was a high degree of uncertainty among the respondents about whether primary care healthcare professionals are well-presented on the NICE committees (figure 5.5).

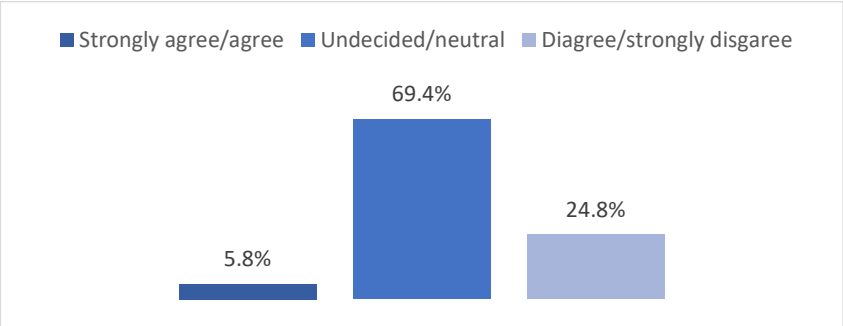
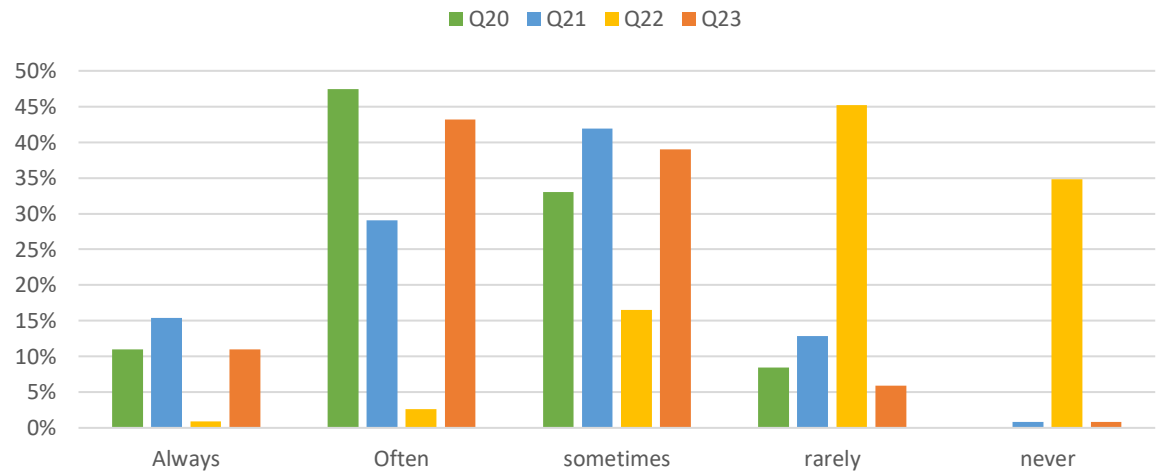


Figure 5.5 Participants' perception of opportunities adequate representation of primary care on the NICE committees (question 13).

5.2.2.1 Information sources

Figure 5.6 shows the prescribers' choice of information sources when they make prescribing decisions. Similar to the findings from the qualitative study (study 1), resources obtained through various training courses were frequently mentioned. It was also observed that recommendations by pharmaceutical sales representatives were hardly used to make prescribing decisions.



Green bars represent percentages healthcare professionals mainly using resources obtained through courses (question 20). Blue bars represent percentages healthcare professionals mainly following the recommendations of the latest published clinical trials (question 21). Yellow bars represent percentages healthcare professionals mainly following recommendations by pharmaceutical sales representatives (question 22). Orange bars represent percentages healthcare professionals mainly following recommendations from the secondary care diabetes team (question 23).

Figure 5.6 Use of information sources when prescribing (score 1 to 5 on Likert scale).

5.2.3 Clinical management of adults with type 2 diabetes

5.2.3.1 Diet and exercise

The participants were also asked if they would prescribe diet and exercise for their patients (table 5.6). Between 87% and 95% of the respondents answered that they *always, often* or *sometimes* offer diet

and exercise *before* or *along with* initiating pharmacological treatment to their patients. A very small fraction of respondents answered *rarely* or *never* in response to question 14 and question 15.

A Chi-Square test of independence indicated *no* significant difference in the proportion of GPs versus other healthcare professionals who would offer diet and exercise *before* or *along with* pharmacological treatment.

Table 5.6 Prescription of diet and exercise for patient with type 2 diabetes

Statements	*n*	Always/ Often	Sometimes	Rarely/Never	General practitioners versus other healthcare professionals, *p*-value [a,b]
When a patient is first diagnosed with T2D do you offer diet and exercise as an intervention before initiating pharmacological treatment?	124	78(62.9%)	30(24.2%)	16(12.9%)	0.326
When a patient is first diagnosed with T2D do you offer diet and exercise along with pharmacological treatment?	124	75(60.5%)	43(34.7%)	6(4.8%)	0.859

5.2.3.2 Preferred choice of antidiabetic drug classes

The most commonly self-reported drug choice at treatment initiation was metformin (97.6%). The preferred choices at first treatment intensification were sodium-glucose co-transporter 2 inhibitors (SGLT-2i) (41.6%) followed by dipeptidyl peptidase-4 inhibitors (DDP-4i) (21.6%) and sulfonylurea (20.8%). The preferred choices at second treatment intensification were SGLT-2i (27.2%), glucagon-like peptide 1 receptor agonists (GLP-1RA) (25.6%) and DDP-4i (19.2%). The remaining respondents chose another drug class. Appendix 21 shows the respondents self-reported preferred choice of drug classes during treatment initiation, first and second treatment intensification if comorbidities/ contraindications/patient preferences were not an issue.

Thirty different patterns of usage were identified from the healthcare professionals self-reported drug choices (table 5.7). The four most commonly reported pathways were metformin, SGLT-2i, GLP-1RA (n=26), metformin, DDP-4i, SGLT-2i (n=15), metformin, SGLT-2i, DDP-4i (n=13) and metformin, sulfonylurea, SGLT-2i (n=10).

Table 5.7 Healthcare professionals' self-reported drug prescribing pathways.

Treatment initiation	First intensification	Second intensification	*n*
Metformin	Metformin	Metformin	(1)
Metformin	Metformin	Sulfonylurea	(4)
Metformin	Metformin	Sodium-glucose co-transporter 2 inhibitors	(4)
Metformin	Metformin	Glucagon-like peptide 1 receptor agonists	(1)
Metformin	Metformin	Insulin	(1)
Metformin	Metformin	Dipeptidyl peptidase-4 inhibitors	(3)
Metformin	Sulfonylurea	Sulfonylurea	(2)
Metformin	Sulfonylurea	Thiazolidinediones	(2)
Metformin	Sulfonylurea	Sodium-glucose co-transporter 2 inhibitors	(10)
Metformin	Sulfonylurea	Glucagon-like peptide 1 receptor agonists	(2)
Metformin	Sulfonylurea	Insulin	(2)
Metformin	Sulfonylurea	Dipeptidyl peptidase-4 inhibitors	(7)

Metformin	Thiazolidinediones	Sodium-glucose co-transporter 2 inhibitors	(1)
Metformin	Thiazolidinediones	Dipeptidyl peptidase-4 inhibitors	(1)
Metformin	Sodium-glucose co-transporter 2 inhibitors	Sulfonylurea	(8)
Metformin	Sodium-glucose co-transporter 2 inhibitors	Thiazolidinediones	(1)
Metformin	Sodium-glucose co-transporter 2 inhibitors	Sodium-glucose co-transporter 2 inhibitors	(1)
Metformin	Sodium-glucose co-transporter 2 inhibitors	Glucagon-like peptide 1 receptor agonists	(26)
Metformin	Sodium-glucose co-transporter 2 inhibitors	Insulin	(1)
Metformin	Sodium-glucose co-transporter 2 inhibitors	Dipeptidyl peptidase-4 inhibitors	(13)
Metformin	Glucagon-like peptide 1 receptor agonists	Sulfonylurea	(1)
Metformin	Glucagon-like peptide 1 receptor agonists	Sodium-glucose co-transporter 2 inhibitors	(2)
Metformin	Dipeptidyl peptidase-4 inhibitors	Metformin	(1)
Metformin	Dipeptidyl peptidase-4 inhibitors	Sulfonylurea	(6)
Metformin	Dipeptidyl peptidase-4 inhibitors	Sodium-glucose co-transporter 2 inhibitors	(15)
Metformin	Dipeptidyl peptidase-4 inhibitors	Glucagon-like peptide 1 receptor agonists	(2)
Metformin	Dipeptidyl peptidase-4 inhibitors	Dipeptidyl peptidase-4 inhibitors	(1)
Sulfonylurea	Metformin	Metformin	(1)
Sulfonylurea	Dipeptidyl peptidase-4 inhibitors	Sulfonylurea	(1)
Dipeptidyl peptidase-4 inhibitors	Dipeptidyl peptidase-4 inhibitors	Sulfonylurea	(1)

5.2.3.3 Consideration when choosing between which antidiabetic drug classes to prescribe

Major consideration when choosing between which antidiabetic drug class to prescribe are presented in figure 5.7. Most of the healthcare professionals consider assessment of patient's individual clinical circumstances (92.6%) when choosing a medicine. Likewise, proven clinical effectiveness of the drug (80.3%) and extent of HbA1c elevation (64.8%) were reported to be important variables which influenced their drug choice.

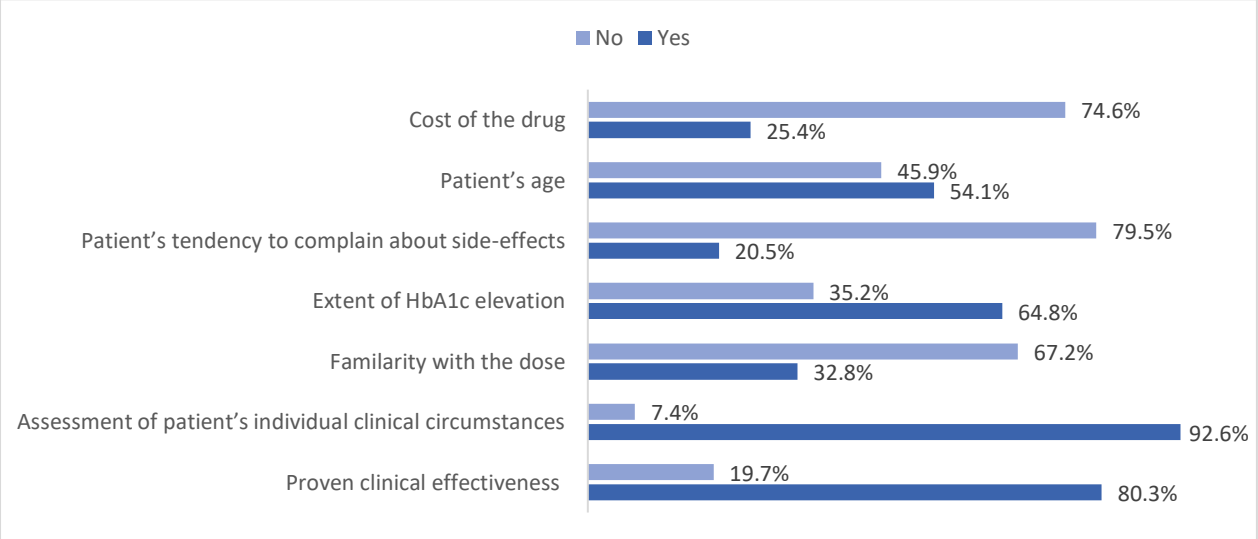


Figure 5.7 Major consideration when choosing which drug to prescribe (question 19, multiple choice).

5.2.4 Insulin prescribing practices

As depicted in figure 5.8 only about half of the respondents from each profession initiates insulin.

A chi-square test for independence indicated *no* significant difference in the self-reported insulin prescribing practices of GPs versus other healthcare professionals (table 5.8, question 24).

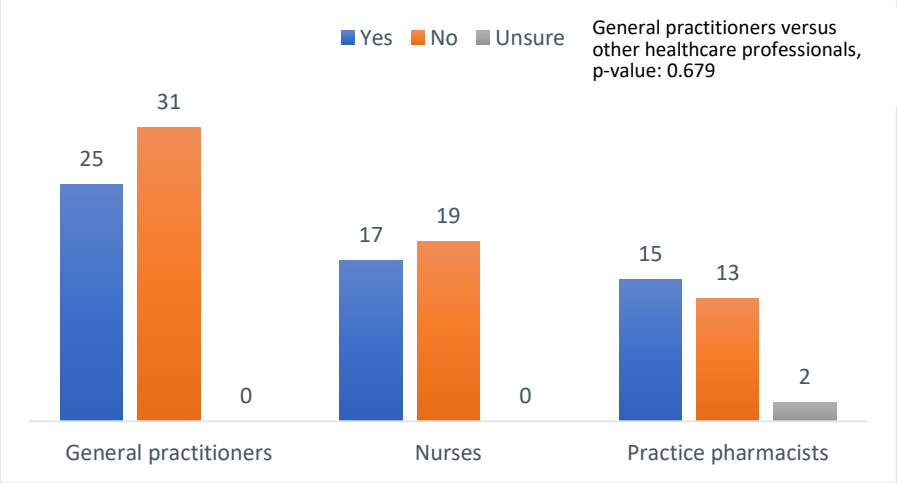


Figure 5.8 Insulin initiation by profession.

Furthermore, it was also found that 22% of the respondents were the only clinicians in the practice who would initiate insulin for their patients in general practice (table 5.8). Another 23.6% of the respondents stated that they would not initiate insulin themselves however one or more of their colleagues would initiate insulin for patients in their general practice.

Table 5.8 Healthcare professionals' insulin prescribing practices

Statements	*N*	Yes	No	Unsure	General practitioners versus other healthcare professionals, p-value [a,b]
I initiate insulin prescribing but none of my colleagues do	114	25(22.0%)	86(75.4%)	3(2.6%)	0.380
I initiate insulin prescribing but some of my colleagues do [c]	110	26(23.6%)	79(71.8%)	5(4.6%)	0.802
I initiate insulin under the instruction of another prescriber i.e. supervised	114	32(28.1%)	81(71.0%)	1(0.9%)	0.584

[a] **p-value calculated through the Chi-square test.**
[b] **p < 0.05 considered statistically significant results.**
[c] **question reversed**

Of those who initiated insulin therapy the majority of the healthcare professionals would initiate the patient on monotherapy (figure 5.9.

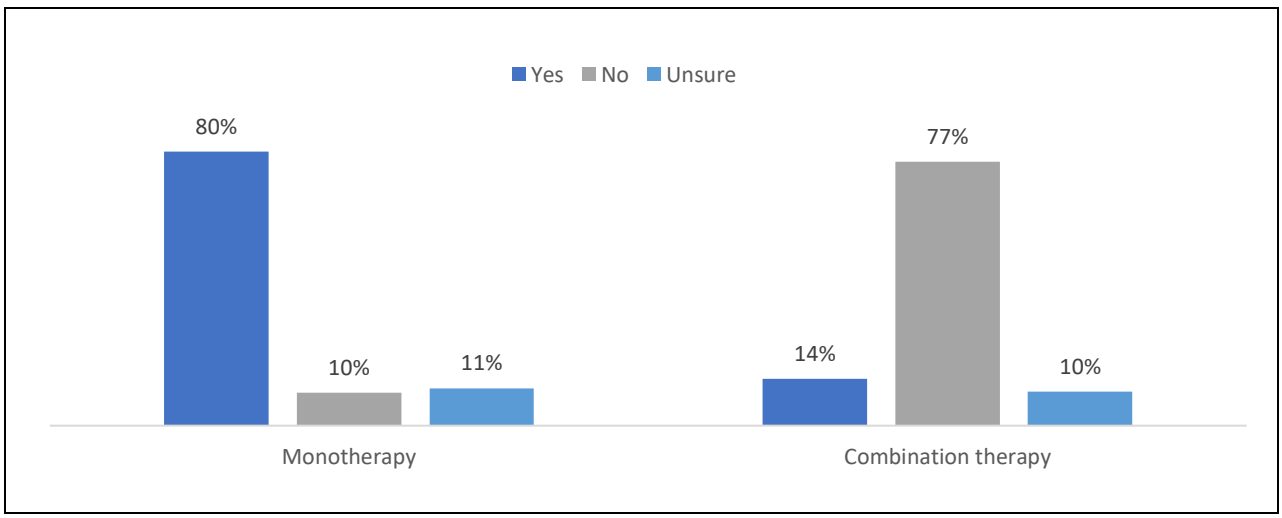
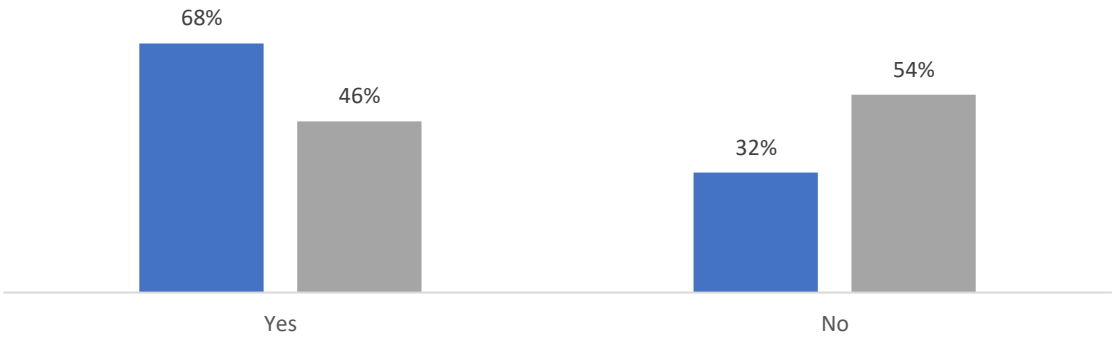


Figure 5.9 Insulin initiation practices.

The respondents reported that they are more likely to refer patients for insulin initiation to an internal diabetes care team than an external diabetes care team (figure 5.10). A chi-square test for independence indicated *no* significant differences in the self-reported referrals pathways used by GPs versus other healthcare professionals.



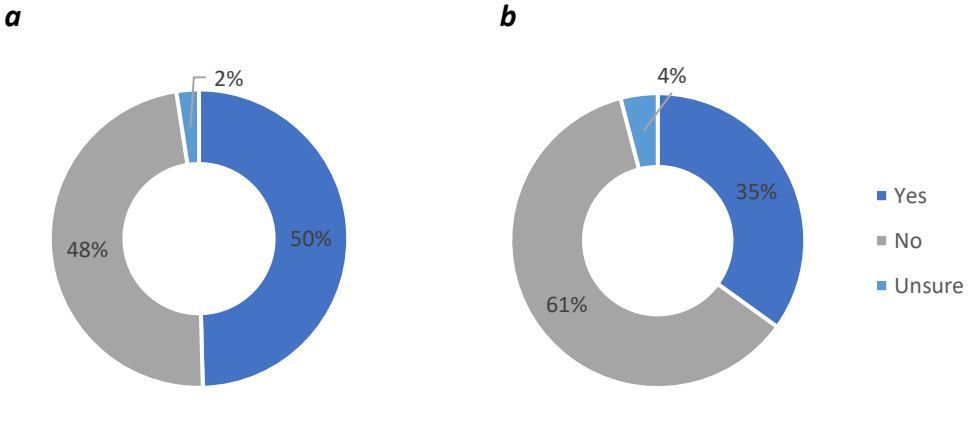
Blue bars represent percentages healthcare professionals who would refer to an internal diabetes care team (questions 28). Grey bars represent percentages healthcare who would refer to an external diabetes care team (question 29).

Figure 5.10 Healthcare professionals' preferred referral route for insulin initiation.

5.2.5 Prescribing Cost of Type 2 diabetes Medicines

5.2.5.1 The influence of medicine cost on prescribing decisions

In the qualitative interviews (study 1) it was reported that the price of medicines shown on the prescribing software could impact their prescribing decision. In the quantitative study the participants were also asked if they consider the price of medicine when prescribing for their patients and 50% reported that they considered the price of the medicine when prescribing for their patients (figure 5.11a).



a In general, do you consider price of a medicine when prescribing for patients with type 2 diabetes mellitus? ***b*** Do you compare the cost of new and old antidiabetic drugs?

Figure 5.11 Considerations given to the cost of medicines when making prescribing decisions (questions 38-39)

Study 1 found that that older medicines were cheaper than newer medicines and for this reason they would try out older medicines before starting patient on newer medicines. When the respondents were asked if they generally compared the prices of new and old antidiabetic drugs, 35% of the respondents reported that they did and 61% did not (figure 5.11*b*).

5.2.5.2 *The influence of Clinical Commissioning Groups on prescribing decisions*

The majority of the respondents reported that their local CCG has an influence on their prescribing of generic brands (77.2%). Similarly, 64.2% of the respondents' reported that their local CCG has an influence on which drug class they prescribe from (table 5.9). They further reported that their local CCGs would provide them with information about the cost of the antidiabetic medicines (68.3%). Sixty two percent of the respondents reported that their practice receive quarterly evaluation on their medicine's expenditures. There was mixed reporting as to if the recommendations provided by the local CCGs reduce the prescribing cost of antidiabetic medicines (*yes*=35.0%, *no*=33.3%, *unsure*=31.7%). Similarly, there were mixed views on if the quarterly evaluations encourage appropriate use of medicines (*yes*=40.0%, *no*=31.7%, *unsure*=28.3%).

Table 5.9 The influence of Clinical Commissioning Groups on prescribing decisions.

Statements	n	Yes	No	Unsure	General practitioners versus other healthcare professionals, p-value [a,b]
Does your local CCG medicine management team guide you on which *generic brand* to prescribe based on the cost of medicines?	123	95(77.2%)	21(17.1%)	7(5.7%)	0.299
Does your local CCG medicine management team guide you on which *drug class* to prescribe based on the cost of medicines?	123	79(64.2%)	30(24.4%)	14(11.4%)	0.674
Does your local CCG medicine management team guide you about the value of the prescribed medicines e.g. cost?	123	84(68.3%)	25(20.3%)	14(11.4%)	0.442
Does your practice receive a quarterly evaluation from the local CCG medicine management team?	122	76(62.3%)	25(20.5%)	21(17.2%)	0.759
In your opinion, is the quarterly evaluation by the local CCG an effective mechanism to contain (reduce) cost?	120	42(35.0%)	40(33.3%)	38(31.7%)	0.558
In your opinion, does the quarterly evaluation by the local CCG encourage appropriate use of medicines?	120	48(40.0%)	38(31.7%)	34(28.3%)	0.941

5.3 Summary of study 2

This study is the second study of the exploratory mixed-methods study. The overall aim of this mixed-methods study was to explore antidiabetic medicines prescribing practices among primary care clinicians in Northern England.

A total of 125 valid questionnaires were received from GPs (46%), nurses (31%) and practice pharmacists (16%) during the survey period. The healthcare professionals were working in general practices across 47 CCGs in Northern England. The majority of the respondents (80%) were able to write prescriptions for their patients. Similar to study 1, this study showed that GPs most often are involved in the primary care teams treating patients with T2D.

1. ***Which prescribing guidelines do primary care clinicians use during their day-to-day prescribing?***

In the past two weeks 18.6% had used NG28, 28.9%% had used ADA- EASD consensus report and 36.8% had used their local CCG formulary when making prescribing decisions. Eighty four percent (84%) of the respondents reported that they feel confident prescribing for patients using NG28. However, the respondents had varying views on whether NG28 was up-to-date with current evidence at the time of publication. Less than one fifth (17.1%) found NG28 to be up-to-date with scientific evidence at the time of the survey. About half (47.6%) of the respondents agreed or strongly agreed that the drugs recommended in NG28 were adequate to treat patients with T2D. Further, 46.7% of the respondents agreed or strongly agreed on that NICE has taken longer to update the guidelines on management of adults with T2D compared to their local CCGs.

There were mixed views on if NICE is effective in managing the budget for medicines and recommends the widest possible range of medicines from the available funds. Moreover, the majority of the respondents were neutral regarding if they were given sufficient opportunity to make their concerns about prescribing recommendations known to NICE. A similar trend was seen for how well-represented primary care practitioners are on the NICE committees.

2. ***How do primary care clinicians manage adults with T2D?***

The respondents reported to frequently offer their patients' diet and exercise *before* or *along with* pharmacological treatment. A Chi-Square test of independence indicated *no* significant difference in the proportion of GPs versus other healthcare professionals who would offer diet and exercise *before* or *along with* pharmacological treatment.

The preferred choices at first treatment intensification were sodium-glucose co-transporter 2 inhibitors (SGLT-2i) (41.6%) followed by dipeptidyl peptidase-4 inhibitors (DDP-4i) (21.6%) and sulfonylurea (20.8%). The preferred choices at second treatment intensification were SGLT-2i (27.2%), glucagon-like peptide 1 receptor agonists (GLP-1RA) (25.6%) and DDP-4i (19.2%). Further, thirty different

patterns of usage were identified from the respondents self-reported drug choices. The most commonly reported pathway for use of was metformin, SGLT-2i, GLP-1RA (n=26).

The three most frequently reported variables considered when choosing a medicine was assessment of patient's individual clinical circumstances (92.6%), proven clinical effectiveness of the drug (80.3%) and the extent of HbA1c elevation (64.8%).

The most frequently reported person to seek advice regarding prescribing within primary care setting was to ask a diabetes specialist nurse (54%). A Chi-Square test of independence indicated significant differences in the proportion of GPs versus other healthcare professionals who would seek guidance regarding which medication to choose from another GP, X^2 (1, N = 112) = 8.92, p = 0.03. When secondary care was contacted it most often was by contacting secondary care diabetes team and asking for advice (62%). The respondents often/always sought help from other healthcare professionals when patients presented with specific or difficult problems (63%), uncertainty of the therapeutic needs of the patient (44.3%) and polypharmacy concerns (34.7%). A Chi-Square test of independence indicated significant difference in the proportion of GPs versus other healthcare professionals who would seek guidance regarding *patient presents with adverse drug reactions* , X^2 (1,N = 106) = 8.85, p = 0.012 and *patient presents with specific or difficult problems* , X^2 (1,N = 110) = 8.41, p = 0.015.

3. How common is insulin initiation in primary care?

Only about half of the respondents from each profession were able to initiate insulin. 22% of the respondents were the only person within the practice to initiate insulin. Among those respondents who did not initiate insulin 23.6% had a colleague within the practice who could initiate insulin. A chi-square test for independence indicated *no* significant difference in the self-reported insulin prescribing practices of GPs versus other healthcare professionals. Of those respondents who initiated insulin, 80% would initiate insulin as monotherapy, and 14% would initiate insulin as combination therapy. Overall, the respondents were more likely to refer patients for insulin initiation to an internal diabetes care team (68%) than an external diabetes care team (32%).

4. Which cost factors were considered when making antidiabetic prescribing choices?

Fifty per cent (50%) of the respondents considered the price of medicine when making prescribing choices. About one third of the respondents (35%) compared the price of older and newer medicines when making prescribing choices.

77.2% of the respondents reported that the local CCG influence them to prescribe generic brands. 64.2% of the respondents reported that local CCG influenced which drug class they would prescribe. Sixty-two percentage (62%) of the respondents reported that the local CCG provide their practice with quarterly evaluations of their medicine expenditures.

CHAPTER 6

Study 3: Price of once-weekly semaglutide versus once-daily liraglutide in a cross-national case study

6.1 Introduction

6.2Introduction

In the previous studies of the mixed-methods research (study 1 and study 2) the antidiabetic medicines prescribing practices of primary care clinicians were explored. This case study investigates the price of treatment with two glucagon-like peptide 1 receptor agonists (GLP-1RA) treatments across 27 European Union (EU) Member States, Norway, Switzerland and United Kingdom. The findings from this chapter will be discussed in chapter 7 along with the findings from study 1 and study 2.

6.1.1 Qualitative findings that informed the conduct of study 3

In study 1, GLP-1RA were often identified as "newer medicines" and "the injection which is not insulin". General practitioners (GPs) mentioned that they started to use the newly available treatment, Ozempic, for their patients instead of once-daily liraglutide as they found that it had better clinical benefits in terms of glucose lowering benefits and weight loss benefits. Further, some GPs reported that their local consultants recommended them to use more expensive GLP-RA treatments as they had better efficacy. Experienced GPs added that they were prescribing GLP-RAs slightly earlier than recommended in National Institute for Health and Care Excellence' (NICE) type 2 diabetes (T2D) guideline. Additionally, informal discussions between the researcher and Clinical Commissioning Groups (CCG) leads and medicine optimisation pharmacists from the geographical research area indicated that many CCGs were carrying out a switch from using Victoza to Semaglutide due to the added clinical benefits. Based on these observations it was decided to survey the price of liraglutide versus semaglutide in a cross-national case study. Vogler et al. has identified ex-factory price, pharmacy purchasing price and pharmacy retail price as important components which determines pharmaceutical expenditure in a country (Vogler, 2019; Vogler, Leopold, Zimmermann, Habl, & de Joncheere, 2014).

6.1.2 Aims and objectives

This study aims to survey the price of treatment with once-daily liraglutide 1.2 mg versus once-weekly semaglutide 1.0 mg in 27 EU Member States, Norway, Switzerland and United Kingdom. The objectives for this study are as follow:

- To conduct a comparative analysis of the ex-factory to determine price differences between countries.
- To calculate the of annual cost of treatment maintenance, and to determine price differences between countries.

The findings from this case study will be discussed in chapter 7 in context of national prescribing policies and clinical benefits of treatment.

6.2 Methodology

This section describes the methodology used to survey the two selected antidiabetic medicines and the medicine price data source.

6.2.1 Antidiabetic medicines description

The license for Victoza (liraglutide) indicate a maximum dose of 3 mg (EMA, 2009). The likelihood of gastrointestinal side-effects can be reduced by titrating the dose of liraglutide. Treatment initiation would happen at 0.6 mg with a weekly increment of 0.6 mg up to 3.0 mg. The vials come as packs of 2 or 3 pre-filled injections (EMA, 2009). The maximum dose for the once-weekly product of Ozempic (semaglutide) is 1 mg (EMA, 2018). The product comes as packs of 1 pre-filed injectable. Table 6.1 shows the drugs and strength compared in this case study.

Table 6.1 Overview of dose, strengths and formulation of Victoza and Ozempic.

Drug class	British National Formulary Chemical Name	Brand name
Glucagon-like peptide 1 receptor agonists	Liraglutide	Victoza 6mg/ml 3ml pre-filled pen
Glucagon-like peptide 1 receptor agonists	Semaglutide	Ozempic 0.25mg/0.19ml 1.5ml pre-filled pen
Glucagon-like peptide 1 receptor agonists	Semaglutide	Ozempic 0.5mg/0.37ml 1.5ml pre-filled pen
Glucagon-like peptide 1 receptor agonists	Semaglutide	Ozempic 1mg/0.74ml 3ml pre-filled pen

6.2.2 Medicine Price Data Source

Price information to conduct price studies can be obtained from various resources. This could be national databases of the country or from larger data collection centres who against payment can provide the relevant data. The most commonly known paid data provider is IQVIA (IQVIA, n.d.). The price information for this study was gathered by the Pharma Price Information (PPI) service located at the Austrian Public Health Institute (Pharma Price Information, n.d.). The PPI services collate data for EU member states (plus Switzerland, Norway and United Kingdom) and has previously been used in reports and publication of surveys comparing differences between the price of medicines (Scneider, 2019). The collected prices are the official prices as published by the pricing authorities in each country without considering discounts and rebates (Pharma Price Information, n.d.).

6.3 Study methods

6.3.1 Research ethics

This study used pre-collected data and did not require any ethical approval.

6.3.2 Comparison of ex-factory level prices

6.3.2.1 Sample selection

The choice of medicines was based on their approved indication by the European Medicines Agency (EMA). Both Victoza and Ozempic are indicated for use in adults with T2D to improve glycaemic control in patients whose T2D is not controlled satisfactory (EMA, 2009, 2018). As the titration of semaglutide

to maintenance dose require different strengths of the medicines all three strengths were surveyed (semaglutide of 0.25 mg, semaglutide 0.50 mg, semaglutide 1 mg). The same medicine can be used to titrate liraglutide to maintenance dose and hence only liraglutide 1.8 mg has been surveyed.

6.3.2.2 Country selection

For the purpose of this study available pharmaceutical pricing data (ex-factory level prices) were acquired for 30 countries in the World Health Organization (WHO) European Region (WHO). The countries which were included were based on convenience sampling (Bruce, 2018). In cases where pricing data for a medicine was not available in a given this country it was excluded from further analyses of the drug, however this was not exclusion criteria from the overall study.

6.3.2.3 Data source

The PPI services extract provided a price list of the selected medicines. The ex-factory prices (manufacturer selling price) of and liraglutide 1.8 mg prices were provided as of September 2019 prices and the ex-factory prices of semaglutide 0.25 mg, semaglutide 0.50 mg, semaglutide 1 mg prices were provided as of February 2020 prices. .

Table 6.2 is an overview of background information for the selected drugs included in the analysis. The presentation on each drug included in the analysis (strength, formulation and quantity). The selection of quantity was guided by practical data availability. Countries which has provided the price of a different pack size than the selected presentation was included in the analysis and a note has been made about this in table 6.2. The PPI services defined the selected drugs as per Anatomical Therapeutic Chemical (ATC) codes according to the WHO classifications. Further, in Cyprus, Denmark, Finland, Netherlands, Sweden and United Kingdom the ex-factory prices are computed via average wholesale mark-ups/margins therefore slight deviations may occur from real-world prices.

The doses per pen are as per recommendation in the product information labels as per marketing authorisation in Europe. To ensure comparability across drugs a number of assumptions have been made; costs for needles for all strengths of semaglutide 1.0 mg are included in the pack and therefore the costs related to the needles are already accounted for. The cost of needles for liraglutide 1.2 mg are *not* included in the pack, however for simplicity these are not included as additional cost. It is assumed that patients are fully adhering (100%) to the prescribed treatment regimens. The cost of self-monitoring is assumed to be the same regardless of which clinical treatment the patient is given and for this reason this has not been included as an additional cost.

Calculation of unit prices (€)

The ex-factory level prices for each medicine was provided in the local currencies of each country and received as a Microsoft Excel workbook from the PPI services. The researcher exchanged all local

currencies to Euros (€) using the average exchange rates from the European central bank (European Central Bank) as of September 2019 and February 2020 for liraglutide and semaglutide, respectively.

Table 6.2 Background information about drugs included in the analysis, selected presentation and unit prices.

		Liraglutide 1.2 mg	Semaglutide 0.25 mg	Semaglutide 0.5 mg	Semaglutide 1.0 mg
ATC*		A10AD05	A10BJ06	A10BJ06	A10BJ06
Type 2 diabetes-related indication		used in addition to diet and exercise	used in addition to diet and exercise	used in addition to diet and exercise	used in addition to diet and exercise
Brand name		Victoza	Ozempic	Ozempic	Ozempic
Company		Novo Nordisk	Novo Nordisk	Novo Nordisk	Novo Nordisk
Year of marketing authorisation		2009	2018	2018	2018
Presentation included in the analysis		Two pens containing 6mg/ml solution for injection. 3ml prefilled pen. 15 doses per pen.	One pen containing 1.34mg/ml solution for injection. 1.5ml pre-filled pens. 8 doses per pen.	One pen containing 1.34mg/ml solution for injection 1.5mL pre-filled pens. 4 doses per pen.	One pen containing 1.34mg/ml solution for injection. 3ml pre-filled pen. 4 doses per pen.
	Variation in countries	Belgium, Greece, Norway and Romania: 3 pens	-	-	Germany 3 pens
	Price as of	Sep-19	Feb-20	Feb-20	Feb-20
	Unit price as	per pen	per pen	per pen	per pen

6.3.3 Annual cost of treatment maintenance

Ex-factory level prices for each country was obtained from PPI services and calculated as described above. The annual cost of treatment of maintenance with once-weekly semaglutide 1.0 mg and once-daily liraglutide 1.2 mg was based on following assumption: once dose-escalation regimen has been carried out patients are maintained on once-daily liraglutide 1.2 mg and once-weekly semaglutide 1.0 mg; one pen of semaglutide 1.0 mg delivers 4 doses and one pen of liraglutide 1.2 mg delivers 15 doses (table 6.2). The cost ratio between the two treatments was calculated by dividing the price of liraglutide 1.2 mg with semaglutide 1.0 mg. For new users of the treatment a cost ratio less than 1 indicates that the treatment with semaglutide is cost saving. A cost ratio more than 1 indicates that the treatment with semaglutide is not cost saving.

6.3.4 Statistical analysis

The data were analysed using SPSS version 24 with 0.05 as level of significance. The sample was summarised descriptively. A series of analyses of variance (ANOVAs) were conducted on the data relating to each drug in turn, to assess the effect of country characteristics on ex-factory unit pricing. With no a priori hypotheses, a Bonferroni correction for multiple comparisons was applied in the interpretation of significance levels of both ANOVAs.

6.4 Findings

6.4.1 Country demographics

The countries which the ex-factory unit prices of once-daily liraglutide 1.2 mg and once-weekly semaglutide 1.0 mg are presented in figure 6.1.

Figure 6.1 World map showing countries which medicine prices were collected from.

The countries featured in the sample are summarised descriptively in Table 2. Sixty two per cent (n = 18) were Western Europe and 38% (n = 11) were from Eastern Europe according the World Bank income group definition (table 6.3).

Table 6.3 Descriptive summary of included countries

Country	Geographical location designation	GDP per capita
Austria	Western	€40,258
Belgium	Western	€37,768
Bulgaria	Eastern	€5,838

Switzerland	Western	€81,270
Cyprus	Western	€15,794
Czechia	Eastern	€15,604
Germany	Western	€38,436
Denmark	Western	€48,102
Estonia	Eastern	€15,269
Greece	Western	€15,570
Spain	Western	€23,506
Finland	Western	€38,725
France	Western	€33,916
Croatia	Eastern	€9,918
Hungary	Eastern	€10,860
Ireland	Western	€48,036
Italy	Western	€27,113
Lithuania	Eastern	€11,152
Luxembourg	Western	€103,809
Latvia	Eastern	€10,844
Netherlands	Western	€40,939
Norway	Western	€71,562
Poland	Eastern	€11,207
Portugal	Western	€16,862
Romania	Eastern	€7,471
Sweden	Western	€47,558
Slovenia	Eastern	€18,829
Slovakia	Eastern	€14,391
United Kingdom	Western	€40,871

6.4.2 Comparison of ex-factory level prices across countries

Table 6.4 shows the availability of pharmaceutical pricing data by drug (appendix 22). Ex-factory level prices of liraglutide 1.2 mg were available in 27 countries; ex-factory prices of semaglutide 0.25 mg were available in 23 countries, ex-factory prices of semaglutide 0.50 mg were available in 23 countries and ex-factory prices of semaglutide 1 mg were available in 24 countries. As described in table 6.4 Malta was the only country without pharmaceutical ex-factory pricing data coverage of any of the surveyed drugs.

Table 6.4 Country coverage of ex-factory level prices acquired from Pharma Price Information services.

Country Coverage Ex-factory level prices		
	Number of countries	**Missing data**
Liraglutide 1.2 mg	27	Malta, Poland Slowakia
Semaglutide 0.25 mg	23	Bulgaria, Cyprus, Lithuania, Luxembourg, Malta, Portugal, Romania
Semaglutide 0.50 mg	23	Bulgaria, Cyprus, Lithuania, Luxembourg, Malta, Portugal, Romania
Semaglutide 1.0 mg	24	Bulgaria, Switzerland, Cyprus, Czech Republic, Lithuania, Luxembourg, Malta, Portugal, Romania, Slowakia

Figure 6.2a-d, shows the ex-factory level unit price for the 30 countries by medicines compared to the median price. The median ex-factory level price for liraglutide 1.2 mg was €41.5 per unit (figure 6.2a). The unit price in most countries was found to be around the median ex-factory price in all countries

besides Sweden (€64.85 per unit) and Switzerland €53.51 per unit). The median ex-factory level price for semaglutide 0.25 mg and semaglutide 0.50 mg were €93 per unit (figure 6.2b and 6.2c). The highest ex-factory level price was found in Czech Republic (€125.06 per unit) closely followed by Austria (€124.5 per unit) and lowest is Croatia (€64.84 per unit). The median ex-factory price for semaglutide 1 mg was €92 per unit (figure 6.2d). The highest unit prices were found in Austria (€124.50 per unit) and Denmark (€122.00 per unit).

Model parameters for ANOVA models for individual drug-strength combinations are summarised in table 6.5. The ANOVAs conducted on liraglutide revealed that neither location nor GDP per capita were significantly associated with ex-factory unit costs at the 5% significance level for liraglutide (p=0.853 for location; p=0.157 for GDP per capita) or semaglutide (p=0.321 for location; p=0.793 for GDP per capita). Bonferroni corrections did not affect any inferences. The fit of the data to the model of liraglutide costs was moderate (adjusted-R^2 =0.074). The fit of the data to the model of semaglutide costs was poor (adjusted-R^2=0.000 approximately). All measured generally effect sizes were small or negligible in magnitude.

Table 6.5 ANOVA model parameters

Drug	Variables	F-ratio	Df	p-value	Partial-η^2
Liraglutide (1.2 mg)	Location	0.0351	1,24	0.853	0.001
	GDP per capita	2.13	1,24	0.157	0.082
Semaglutide (1.0 mg)	Location	1.05	1,17	0.321	0.058
	GDP per capita	0.0708	1,17	0.793	0.004

Ex-factory unit cost distributions of both drugs are illustrated in figure 6.3. Liraglutide unit costs have low variability except in two countries, Sweden and Switzerland, where costs are substantially higher than in other countries. Semaglutide unit costs are more variable, and also slightly skewed.

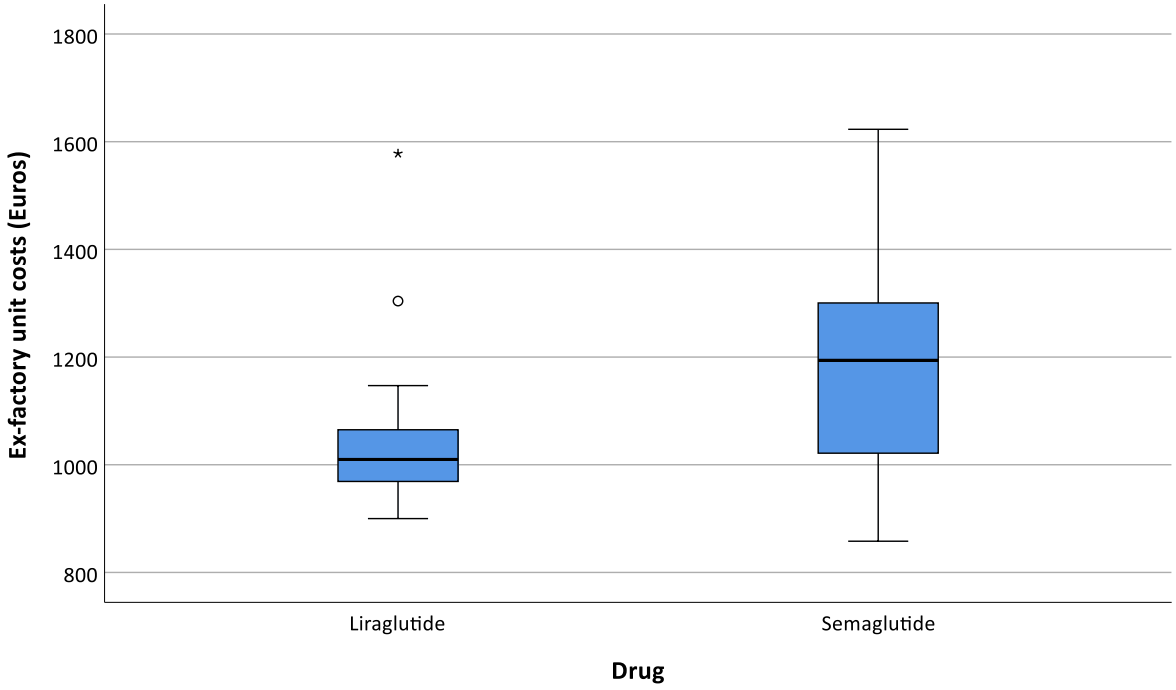
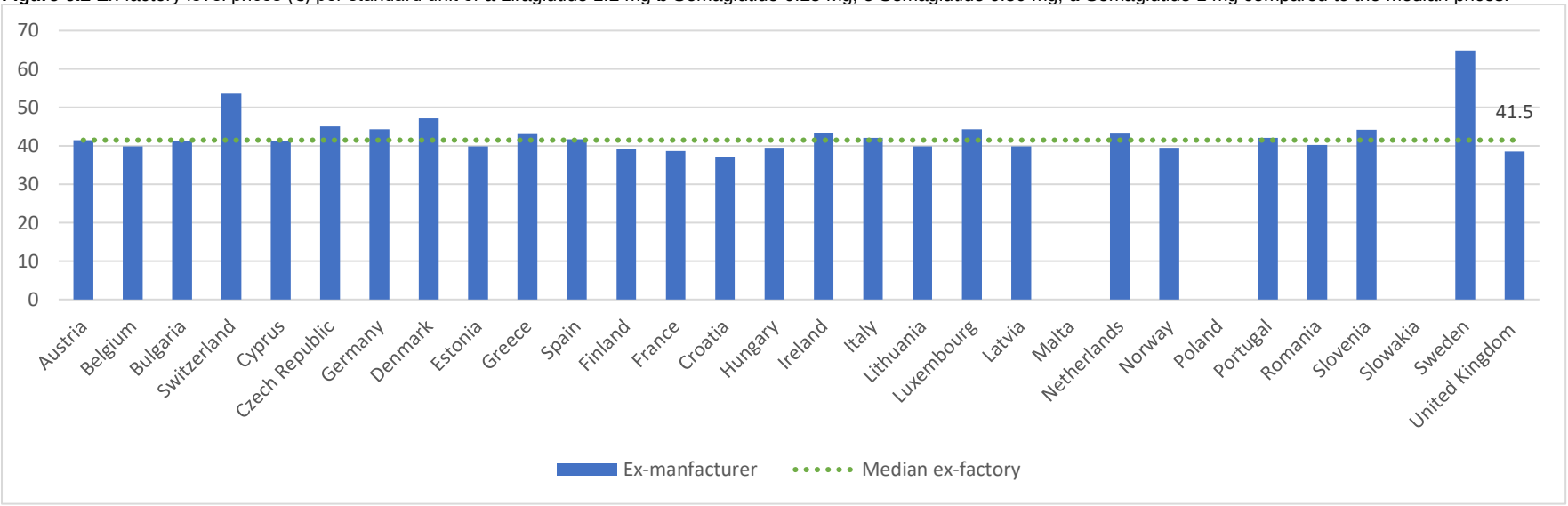
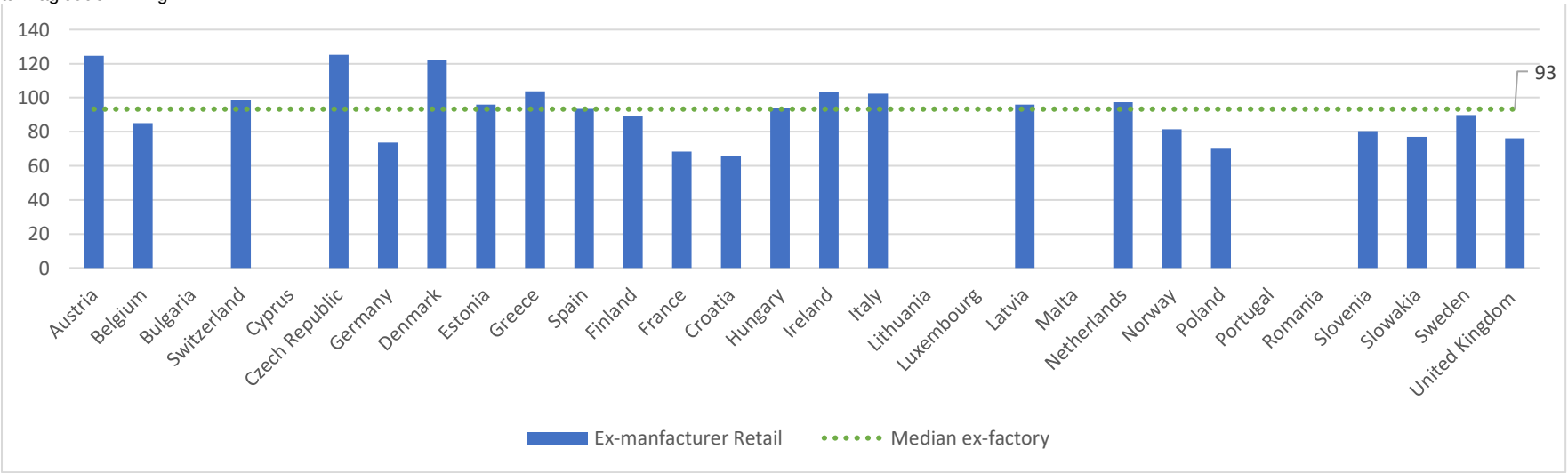


Figure 6.3 Ex-factory unit costs: liraglutide and semaglutide

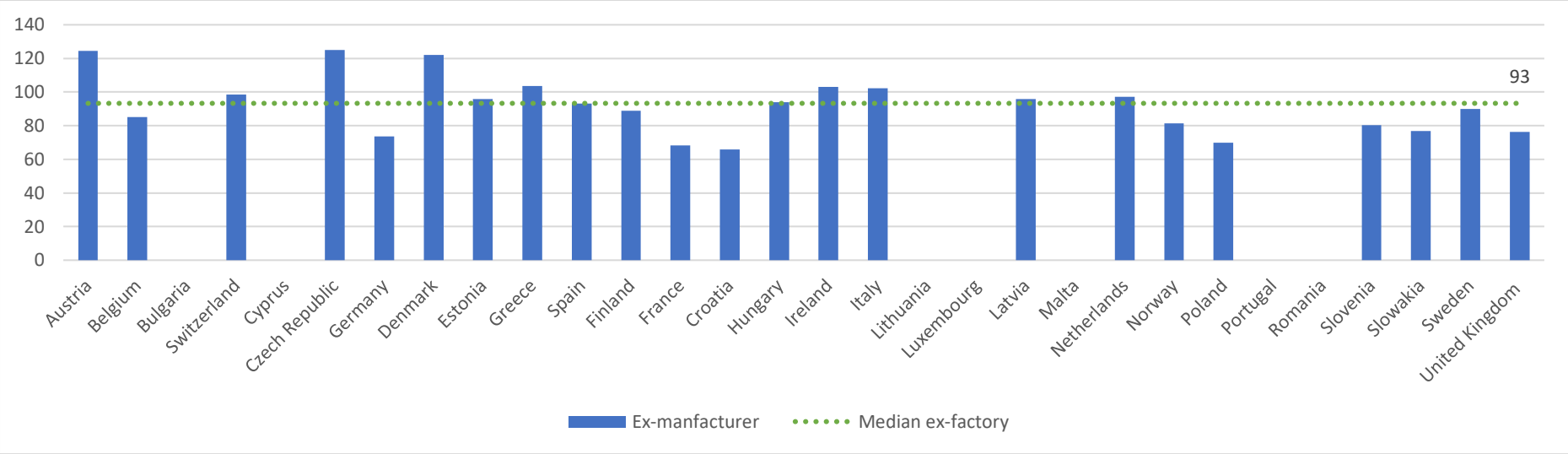
Figure 6.2 Ex-factory level prices (€) per standard unit of **a** Liraglutide 1.2 mg **b** Semaglutide 0.25 mg, **c** Semaglutide 0.50 mg, **d** Semaglutide 1 mg compared to the median prices.



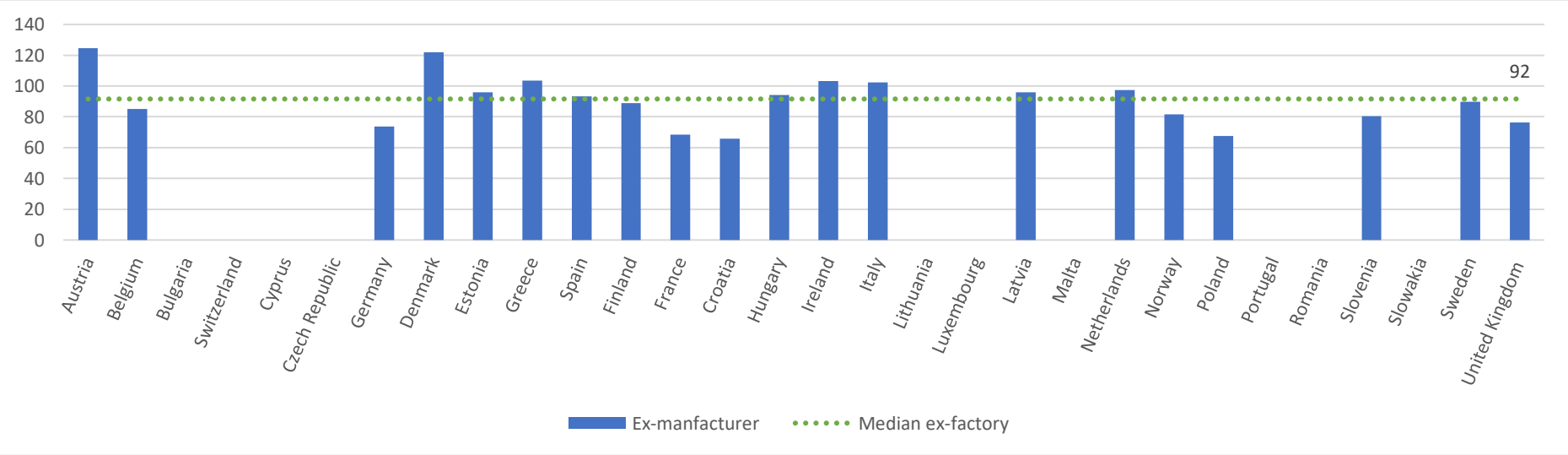
a Liraglutide 1.2 mg



b Semaglutide 0.25 mg



c Semaglutide 0.50 mg



d Semaglutide 1 mg

6.4.3 Annual cost of treatment maintenance

Ex-factory level prices were used to calculate the annual cost of treatment maintenance of once-weekly semaglutide 1.0 mg and once-daily liraglutide 1.2 mg. Table 6.6, shows that the annual cost of treatment maintenance of once-weekly semaglutide 1.0 mg is highest in Austria (€1,623 per year) and lowest in Croatia (€858 per year). The annual cost of treatment maintenance of once-daily liraglutide 1.2 mg was highest in Sweden (€1,578 per year) and lowest in the Croatia (€900 per year).

The cost ratio between once-weekly semaglutide 1.0 mg and once-daily liraglutide 1.2 mg was highest in Austria where treatment maintenance with once-weekly semaglutide 1.0 mg and was found to be 1.6 times more expensive than once-daily liraglutide 1.2 mg. The lowest cost ratio was found in Sweden where once-daily liraglutide 1.2 mg cost 0.74 times the price of once-weekly semaglutide 1.0 mg. Based on the annual cost of treatment maintenance is cost saving to treat patients with of once-weekly semaglutide 1.0 mg in Germany, France, Croatia, Slovenia and Sweden.

Table 6.6 Annual cost of treatment maintenance with once-weekly semaglutide 1.0 mg and once-daily liraglutide 1.2 mg.

	Liraglutide 1.2 mg (€)	Semaglutide 1.0 mg (€)	Difference in price (€)	Cost ratio	
Austria	1,010	1,623	613.11	1.61	⊗
Belgium	970	1,109	139.17	1.14	⊗
Bulgaria	1,005	-	-1,004.50	-	-
Switzerland	1,304	-	-1,304.48	-	-
Cyprus	1,007	-	-1,007.03	-	-
Czech Republic	1,097	-	-1,096.90	-	-
Germany	1,077	960	-117.30	0.89	∅
Denmark	1,147	1,590	442.88	1.39	⊗
Estonia	969	1,249	280.31	1.29	⊗
Greece	1,049	1,351	301.96	1.29	⊗
Spain	1,016	1,216	199.93	1.20	⊗
Finland	951	1,159	207.91	1.22	⊗
France	940	891	-49.28	0.95	∅
Croatia	900	858	-41.75	0.95	∅
Hungary	961	1,226	264.72	1.28	⊗
Ireland	1,053	1,345	291.34	1.28	⊗
Italy	1,023	1,333	310.49	1.30	⊗
Lithuania	969	-	-969.08	-	-
Luxembourg	1,078	-	-1,077.97	-	-
Latvia	969	1,249	280.18	1.29	⊗
Malta	-	-	-	-	-
Netherlands	1,052	1,268	216.26	1.21	⊗
Norway	960	1,062	101.95	1.11	⊗
Poland	-	911	911.40	-	-
Portugal	1,023	-	-1,023.01	-	-
Romania	978	-	-978.20	-	-
Slovenia	1,077	1,049	-28.18	0.97	∅
Slowakia	-	-	0.00	-	-
Sweden	1,578	1,172	-405.74	0.74	∅
United Kingdom (England and Wales)	938	994	55.75	1.06	⊗

Explanation of symbols: ∅ = cost saving; ⊗ = not cost saving

6.5 Summary

This case study compared the unit prices of treatment with once-weekly semaglutide 1.0 mg versus once-daily liraglutide 1.2 mg in 27 EU Member States, Norway, Switzerland and United Kingdom. The study showed that liraglutide 1.2 mg was more frequently available than semaglutide 1.0 mg (27 countries versus 24 countries). The price of ex-factory level prices per unit varied between the surveyed countries. For liraglutide the unit price was mostly stable around the median price (€41.50 per unit). The ex-factory level price of semaglutide 1.0 mg ranged between 65.84 per unit (Croatia) and €124.50 per unit (Austria) with a median price was €92 per unit.

The price of one years' treatment was calculated for countries where both treatment prices (liraglutide 1.2 mg and semaglutide 1.0 mg) were available. The analysis demonstrated that semaglutide 1.0 mg was cost saving in Germany, France, Croatia, Slovenia and Sweden. In the remaining countries the use of semaglutide 1.0 mg was not cost saving. There is no evidence for pricing differentials in either liraglutide or semaglutide across European countries. However, the financial impact of swithing from ligralutide to semaglutide must be seen in context of the added clinical benefits of using semaglutide as well as the negotiated discounts and rebated in each country.

CHAPTER 7

Discussion of findings

7.1 Recap of the mixed-methods study

This chapter begins with a recap of the overall aim of this PhD thesis and each sub-study. This is followed by a general discussion of the key findings from the three sub-studies and discussion of findings in context of existing literature, respectively. Then, recommendations for implementation of use of newer antidiabetic medicines have been provided. Lastly, the strengths and limitations of the methods have been discussed. As the findings from the two systematic literature reviews have already been discussed in detail in chapter 2, they are not discussed in the current chapter. Nevertheless, where appropriate a reference has been made to the findings from the two systematic literature reviews.

The overall aim of this study was to investigate primary care clinicians' antidiabetic medicines prescribing practices. This PhD thesis aimed to answer the following objectives:

- *Objective 1:* Which antidiabetic medicines are prescribed during the management of adults with type 2 diabetes in primary care?
- *Objective 2:* What influences GPs' antidiabetic medicines prescribing decisions in primary care?
- Objective 3: What are the challenges in using antidiabetic medicines in primary care?

Study 1 explored general practitioners' (GPs) type 2 diabetes (T2D) antidiabetic medicines prescribing practices in Northern England. In this study following research questions were answered:

- What is the perceived value of NICE in clinical practice?
- How useful is NG28 when making prescribing decisions during day-to-day prescribing?
- How do the GPs choose between antidiabetic medicines when treating patients with T2D?

To answer these questions a semi-structured interview guide was developed, piloted and used to collect qualitative interview data from primary care GPs. This study was the first of its kind to analyse the experiences of GPs with the use of antidiabetic medicines in a primary care setting. The previous studies were limited to knowledge and skills of secondary care junior doctors' diabetes prescribing practices and retrospective primary care data. This study was also the first study to collect data on the influences of NG28 on the choice of antidiabetic medicines during the consultation with the patient. Prior research had focused on prescribing guidelines in other therapeutic areas and did not produce evidence which could be transferred to NICE T2D prescribing guidelines. Transcripts from the qualitative interviews were thematically analysed and presented in chapter 4. The findings from the qualitative interviews described GPs' prescribing practices in detail, and also provided valuable insight on topics of controversy in the literature which can aid in the development of future policy and practice decisions in the primary care setting. The interviewees had varying professional experience with antidiabetic prescribing and the findings furthered the understanding of factors which influence their prescribing decisions and affect the treatment outcomes of the patients.

The analysis of the qualitative interviews led to the following questions which were sought to be expanded on in study 2:

- Which prescribing guidelines do primary care healthcare professionals use?
- How do primary care clinicians manage adults with T2D?
- How common is insulin initiation in primary care?
- Which cost factors were considered when making antidiabetic prescribing choices?

In order to answer these questions a questionnaire was developed, validated and administered. The self-administered survey was followed by an online data collection. The survey was developed to collect data on the respondents' demographic characteristics, use of prescribing guidelines, clinical management of patients, and cost of antidiabetic medicines. The tool was pre-tested and then piloted by GPs from the qualitative study and two practice pharmacists. Throughout the development process diabetes experts from primary and secondary care were consulted.
The survey is the first of its kind in England to capture data on primary care clinicians' self-reported prescribing practices and the findings were presented in chapter 5. In this phase of the study, the same geographical area was surveyed as study 1 but the target population had been expanded to include nurses and practice pharmacists as per findings from study 1 and recommendations from diabetes experts.

Study 3 is a case study which is also based on the analysis of the qualitative interviews and observations from the systematic literature review on prescribing trends. It was sought to survey the acquisition cost of treatment with once-weekly semaglutide 1.0 mg versus once-daily liraglutide 1.2 mg. The data used in this study was obtained from Pharma Price Information (PPI) services which was used to calculate the annual cost of treatment maintenance across 27 European Union (EU) Member states, Norway, Switzerland and the United Kingdom (UK). The findings from this case study have been presented in chapter 6 and are the first of its kind to analyse price differences across such a large data set.

As described in chapter 3 of this PhD thesis, the development of the interview guide was directed by the findings from the review of literature and the two systematic literature review on prescribing trends and cost of antidiabetic medicines, respectively. Exclusion of existing theoretical frameworks allowed the researcher to let the data drive the research. Yet, after the data analysis had been completed it became evident that identified influences on prescribing decisions were embedded in established macro, meso and micro socio-institutional structure. The theoretical approach has been described in detail in chapter 3. In this chapter the findings are discussed following the hierarchy of healthcare in England and can be described as:

- *Macro levels*: refers to strategic prescribing policy decisions influenced by research evidence (guidelines) and clinical governance mechanisms (NICE).
- *Meso levels:* refers to Clinical Commissioning Groups.
- *Micro levels*: refers to the individual GPs and the decisions made during the consultation with the patient.

7.2 General discussion of key findings

The findings from this PhD thesis are according to the researcher's knowledge, the first to unify qualitative and quantitative findings on antidiabetic medicines prescribing in primary care in England. This study seeks to make a contribution towards reducing the gap between what is known about diabetes care and what is commonly practiced in primary care. The aim of this general discussion is to contextualise and gauge the representativeness of the gathered findings from the three sub-studies before analysing them in context of existing literature. The key findings are organised according to healthcare level and themes generated in study 1 (table 7.1).

7.2.1 Management of adults with type 2 diabetes in primary care

The qualitative study found that the GPs described varying organisational structures. In their daily practices they were mainly supported by nurses and practice pharmacists. In study 2 the respondents indicated that there are more nurses than diabetes specialist nurses and practice pharmacists involved in the primary care teams. The findings from the qualitative and quantitative studies showed that primary care teams were supported by secondary care consultants through referrals and joint clinics to treat patients who needed more complex care. In study 1 a number of reasons for seeking support from primary and secondary healthcare professionals were identified. Among the mentioned reasons, the quantitative study found that other healthcare professionals were often approached when the respondents presented with specific or difficult problems, polypharmacy concerns and uncertainty of the therapeutic needs of the patient.

7.2.2 Use of prescribing guidelines

In the qualitative study, it was observed that GPs we aware of the NICE prescribing guideline (NG28) for managing patients with T2D. However, a high degree of the GPs used other interpretive information sources based on NG28 when making prescribing decisions. The GPs described a number of barriers to implementation of NG28 in clinical practice such as lack of trust in the content of the guidance (outdated choice of medicines), lack of trust in the sources used by the NICE committee (experience favoured over scientific evidence), complex presentation of guidelines (lengthy guideline document and lack of treatment algorithm which helps choose between the available treatments). When the respondents in study 2 were asked which prescribing guidelines they had consulted in the past two weeks the analysis showed that 18.6% had used NG28, 28.9% had used American Diabetes Association-European Association for the Study of Diabetes (ADA-EADS) consensus report and 36.8% had used their local CCG formulary when prescribing for patients with T2D. Resources obtained through various training courses and recommendations from the secondary care diabetes team were the two most frequently used information resources identified by the respondents in the quantitative study.

Although it was clear from the qualitative study that NICE guidance was well-regarded among GPs it was difficult to get a clear picture of to which extent the recommendations from NG28 had been adapted. In the quantitative study about half of the respondents found the drug classes recommended by NICE in the NG28 guideline were adequate to treat patients with T2D. Nevertheless, there seemed to be a

disparity in views on if NG28 was up-to-date with available evidence at the time of publication. Further, about half of the respondents did not find NG28 to be up-to-date with available evidence at the time of the survey. Although the reason for the views on the applicability of NG28 in 2015 and 2019 cannot be deducted from the responses, one can speculate whether the respondents cannot remember due to the four-year difference since the guidance was published. Another possible reason could be that although NICE in 2017 adapted evidence from Health Technology Assessment (HTA) on sodium-glucose co-transporter 2 inhibitors (SGLT-2i) NG28 is still not providing sufficient guidance as compared to CCG formularies and ADA-EADS consensus report which are updated more frequently.
The use of antidiabetic medicines was also influenced by the treatments approved for use in the local CCGs. The local formularies were often described to be updated more frequently than NICE guidance and included evidence from latest clinical trials. Lastly, while making decisions GPs also kept the recommendations in NG28 in mind, however it was noted that the GPs found that the guidance was so flexible that treatments could be chosen in almost any order and would still adhere to the guidance.

7.2.3 Prescribing practices

During the data analysis of study 1 it was noticed that there may be differences in the GPs definitions of 'complex treatment'. GPs experienced with prescribing antidiabetic medicines were confident using the whole range of treatments, and often advised colleagues about their use. Less experienced antidiabetic medicines prescribers were more confident in the first few steps of treatment, and most often described the use of metformin as first-line treatment followed by sulfonylurea or dipeptidyl peptidase-4 inhibitors (DDP-4i) as second-line treatment. Less experienced antidiabetic medicines prescribers would refer patients who needed complex treatment to other primary care healthcare professionals or for outpatient secondary care management.

Study 1 found that the GPs' skills and knowledge about antidiabetic medicines were important predictors of their degree of autonomy when using available treatments. In the quantitative study the majority of the respondents (84.0%) indicated that they felt confident regarding prescribing medicines for adults with T2D based on current guidance provided by the NICE. Further, present findings showed that there was high self-reported preference towards use of SGLT-2i and glucagon-like peptide 1 receptor agonists (GLP-1RA) as second- and third-line treatments. When these findings are linked with the prescribing practices described in the qualitative study, it could indicate that newer antidiabetic medicines, which are more expensive treatments, are often used before older antidiabetic medicines.

During the systematic literature review of prescribing trends in primary care it was noticed that there had been a change in the antidiabetic treatments used in the past twenty years. Metformin and sulfonylurea were described as older treatments with proven efficacy and low cost. The position of thiazolidinediones was a bit more fluid due to concerns about cardiovascular safety. Further, there also seemed to be uncertainty in the positioning of the three most recently introduced drug classes dipeptidyl peptidase-4 inhibitors (DPP-4i), SLGT-2 inhibitors and GLP-1RA due to evolving evidence based on ongoing clinical trials.

In the qualitative study varying insulin prescribing practices were described. In the quantitative study, it was observed that about 40% of the respondents initiated insulin therapy in primary care. Among those who did not initiate insulin about 24% had a colleague in the practice who could initiate insulin.

7.2.4 Characteristics of antidiabetic medicines

The use of antidiabetic medicines was often described in terms of the specific clinical indication of the antidiabetic medicines and the safety profiles. In the qualitative interviews, the participants mentioned a number of factors which they considered when choosing between drug classes. In the quantitative study, the respondents were asked to choose factors which would make them choose one drug class over the other. The most considered reasons for choosing a drug class included assessment of patients individual clinical circumstances (92.6%), proven clinical effectiveness of the drug (80.3%), patients tendency to complain about side-effects (79.5%) and extent of HbA1c elevation (64.8%). These findings align well to the reasons reported in the qualitative study.

7.2.5 Cost of antidiabetic medicines

In the review of literature (chapter 1) there were described differences in the expenditures on antidiabetic medicines across CCGs in England. However, none of the UK studies met the inclusion criteria of the systematic literature review on cost of antidiabetic medicines (chapter 2). Further, it was noticed that it was difficult to compare the cost of antidiabetic medicines as there was no standardised definition of antidiabetic medicines. The qualitative interviews, informal conversations with CCG leads and medicine optimisation pharmacists from the diabetes community led the researcher to understand that various strategies were used to optimise the expenditures on antidiabetic medicines. During the qualitative interviews the two most commonly discussed scenarios were in-class switches of DDP-4i and glucagonlike peptide 1 receptor agonist (GLP-1RA), respectively. As pricing of a drug and the individual country reimbursement policies decide if a drug gets access to a countries drug market (Vogler, 2019) a case study was conducted to compare the price of liraglutide and semaglutide. The results from study 3 are also discussed in context of cost saving measures by CCGs (meso level) and NICE's recommendations on use of GLP-1RA in the respective section under objective 1.

Table 7.1 Key findings of the PhD thesis structured by level and subtheme across study 1 -3.

Level	Subtheme	Study 1 (chapter 4)	Study 2 (chapter 5)	Study 3 (chapter 6)
Macro	Value of NICE in the healthcare system	Using NICE is learnt behaviour. GPs believes in the ethos of NICE. Attitudes to cost-effective prescribing recommendations. Attitudes to evidence-based prescribing recommendations.		
Macro	Perceptions about the NICE committees	Question applicability of recommendations in primary care. Driven by secondary care. Lack of incentive to get involved.	Most respondents were neutral about communication with NICE. Most respondents were neutral about if there is sufficient representation of primary care healthcare professionals in the NICE committees.	
Macro	Knowledge and perceptions of NICE	Old boys' network. Limited knowledge about NICE Guideline Development Groups. GPs cannot challenge recommendations from NICE as individuals. CCGs are more approachable.		
Macro	Views of scientific evidence reviewed by the Guideline Development Group	Doubts if all available evidence was reviewed. Has UKPDS been given too much emphasis? Enough emphasis has not been given to clinical trial and evidence from SLGT-2i.		

Micro	Influences on prescribing choices	Inconsistent use of NG28. NICE guidance is not up-to-date. Vague guidance after metformin. Guidance provided by CCGs is updated more frequently. Differences in recommendations from CCGs. Differences in antidiabetic prescribing behaviours learnt from consultants and hospital prescribing. If a drug is not on the NICE guidance it may not be cost-effective.	Views on adequacy of drugs recommended in NG28. Local formulary most frequently consulted in the last 2 weeks. Time taken to update T2D guideline by NICE and loca CCG. Comparison of cost of newer and older treatments. Resources obtained through courses and recommendations from the secondary care diabetes team are often/always used by most respondents. Recommendations by pharmaceutical sales representatives are rarely used by most respondents.	Semaglutide has added clinical benefits.
Micro	Professional experience with antidiabetic medicines prescribing – diet and lifestyle	Vague description of diet and lifestyle measures. GPs had limited knowledge about how to get on to patient education programs. Diet and lifestyle interventions mostly managed by nurses.	Proportion of patients who are offered diet and lifestyle interventions either before or along with pharmacological treatment.	
Micro	Professional experience with antidiabetic medicines prescribing – stepwise approach to treatment	Experienced antidiabetic medicines prescribers use full range of available treatments. Less experienced antidiabetic prescribers use older treatments including DDP-4i. Experienced antidiabetic medicines prescribers used head-held formularies. Less experienced antidiabetic medicines prescribers adapt knowledge from other information sources. GLP-1RA referred to as injectable which is not insulin. Drug characteristics are important when choosing between available treatments.	Self-reported prescribing patterns. Metformin most common first-line treatment The preferred choices at first treatment intensification were SGLT-2 (41.6%) followed by DDP-4 (21.6%) and sulfonylurea (20.8%). The preferred choices at second treatment intensification were SGLT-2 (27.2%), GLP-1 (25.6%) and DDP-4 (19.2%).	

Micro/ meso	Professional experience with antidiabetic medicines prescribing – insulin prescribing practices	Varying insulin prescribing practices. Resistance towards initiating insulin among some GPs. Insulin is considered last resort of treatment. Variation in types of insulin used across CCGs.	Insulin monotherapy more often prescribed than insulin combination therapy. More GPs than nurses and practice pharmacists initiated insulin. One fifth (20%) of the respondents were the only healthcare professional in the general practice who initiated insulin.	
Micro	Professional confidence with antidiabetic medicines prescribing	All GPs aware of new and old treatment but aim of treatment depends on experience with prescribing antidiabetic treatments. Lack knowledge understanding of HbA1c targets set by NICE.		
Micro	Organisational structure of the general practices	Overlapping roles between primary care GPs and nurses. Experienced nurses are more valuable than non-experienced nurses. Uncertainty about role and skills of pharmacists.	Mostly GPs and nurses. Few diabetes specialists nurses. Few practice pharmacists.	
Micro/ meso	Organisational structure of the general practices	T2D is mainly treated in primary care. Varying referral practices. GPs have had to upskill to follow development. Less experienced antidiabetic medicines prescribers feel they lack guidance and training in use of newer antidiabetic drug classes.	Reasons for seeking guidance from other healthcare professionals regarding appropriate dose, patient presents with adverse drug reactions, patient presents with specific or difficult problems	
Micro	Antidiabetic medicines prescribing practices	Shared-decision making is ideal but not always possible. Patient nonadherence can be avoided by listening to patient requests. Patient concerns explored but no mention of patient education to change perceptions.	Major consideration when choosing which drug to prescribe.	

Micro	Influences on treatment outcomes	Lack of reinforcement of diet and lifestyle measures from clinicians. Patients lack motivation to engage in diet and lifestyle interventions. Several reasons for delay in treatment intensification		
Micro/ meso	Cost-consciousness in prescribing	Influences from CCGs. Resistance towards cost-saving measures Newer drug classes are perceived to be more expensive than older treatments. Older treatments are efficient and should be prescribed before newer treatments. Patients with complex disease can benefit from newer treatments. Treatment review can reduce cost.	Local CCGs influence choice of generic drugs. Local CCGs influence choice of drug classes. Quarterly evaluations are effective to contain cost. Quarterly evaluations encourage appropriate medicines use.	No evidence for pricing differentials in either liraglutide or semaglutide across European countries.
Meso/ macro	Cost reducing interventions	QOF targets does not encourage personalising prescribing.		

Abbreviations: CCGs - Clinical Commissioning Groups: **DDP-4i** - dipeptidyl peptidase-4 inhibitors: **GDG** - Guideline Development Group:

7.3 Discussion of findings in context of existing literature

This section discusses the findings from the mixed-methods study. In each section, it has been specified which research objective is being answered and which sub-study the findings are gathered from.

7.3.1 Objective 1: Which antidiabetic medicines are prescribed during management of adults with type 2 diabetes in primary care?

In this section beliefs and behaviours about glycaemic control and treatment outcomes, diet and exercise, prescribing trends and cost are discussed in context of existing literature. Objective 1 has been answered using findings from sub-studies 1 to 3 as appropriate.

7.3.1.1 Prescribing trends and adherence to prescribing guidelines

This section discusses findings on glycaemic control, diet and exercise, first-, second- and third-line treatment, respectively.

7.3.1.1.1 Glycaemic control and treatment outcomes

Overall, the qualitative study found that there was a pushback against the idea of the patients not being adequately controlled. The National Diabetes Audit (NDA) showed that 67.6% of patients with T2D received NICE key processes of diabetes care in 2013/2014. The percentage of patients who reached the targets had decreased to 58.0% by 2017-2018 and further reduced to 53.8% by 2018-2019 (NHS Digital, 2020b). Moreover, the NDA showed that the percentage of patients who achieved the NICE defined treatment targets for HbA1c ≤58 mmol/mol, 7.5% (66.8% to 66.3%), blood pressure ≤140/80 mm Hg (73.6% to 74.0%) and cholesterol <5 mmol/L (77.8% to 78.2%) were more or less steady between 2013-2014 and 2018-2019. The overall number of patients achieving all three treatment targets was as low as 41.3% in 2018-2019.

Regarding recommended targets in NG28, the GPs observed that the guidance did not provide sufficient support to reach these targets. In a study which investigated delivery of care among trainee doctors in the management of diabetes, it was shown that only 41% of the doctors would take initiative to optimise glycaemic control for their patients (George et al., 2011). A recent study conducted in the UK showed that the median time to up-titration of metformin was 175 days regardless of HbA1c level (Iglay et al., 2020). This is in accordance with current recommendations in NG28 which recommends dose optimisation within 6 months (NICE, 2015). However, Iglay et al. also found that 72% of new users of metformin in the UK were initiated on dose value lower than 1,000 mg/day as advised in the product information label (Electronic medicines compendium, 2020). Sixty-nine percent (69%) of the new users stayed on this dose for 6-12 months despite having a HbA1c level above 53 mmol/mol (Iglay et al., 2020). Moreover, a small UK study have suggested lack of titration of oral antidiabetic medicines as reasons for HbA1c levels showing very poor glycaemic control (>86 mmol/mol, ≥10.0%) (Khan, Lasker, & Chowdhury, 2011). Of note, lack of efficacy can be caused by therapy nonadherence and it has also

been found that adherence to metformin is lower than other oral antidiabetic medicines due to gastrointestinal (GI) side-effects (Farmer et al., 2016; White et al., 2011).

Although the GPs said that they are aware of the importance of glycaemic control and more aggressive treatment plans, this study found that GPs did not mention any specific treatment targets, and hence their understanding of aggressive treatment remains unclear. It was explained that the guideline recommendations kept changing and they would check NICE (N28) for its recommendations prior to writing a prescription. One UK study found that at the time of pharmacological treatment initiation 50% of the patients who were initiated on non-insulin antidiabetic medicines had a HbA1c of >65 mmol/mol (8.1%), and 25% had a HbA1c of >80 mmol/mol (9.5%)(Maguire et al., 2014). These findings were well above the recommended HbA1c level of ≤48 mmol/mol (6.5%) in CG87 which was the NICE guidance in place at the time of study (NICE, 2009). The guidance on glucose levels when therapeutic treatment should be initiated is still the same in NG28 (NICE, 2015). This indicates that patients in the UK are initiated on their first antidiabetic medicines later than recommended by NICE.

GPs expressed concerns about the expectation of meeting Quality and Outcomes Framework (QOF) targets and at the same time provide tailored treatment. The GPs reported that NG28 recommended treatment could be relaxed to be tailored to patients (such as the elderly) but following this recommendation would mean they would loose out on QOF payments. Interestingly, a recent study found that general practices with a higher number of older patients (>65 years) on their practice list had a higher proportion of patients who achieved glycaemic target levels (58 mmol/mol, ≤7.5%) (Heald et al., 2018). Additionally, GPs believed that the patients' social status had an impact on their treatment outcomes. GPs working in areas with socially disadvantaged patients found that they had a higher number of patients who did not achieve glycaemic targets. These beliefs are in accordance with previous findings on glycaemic control in disadvantaged patients which showed they have higher HbA1c levels (86 mmol/mol, >10%) (Heald et al., 2018). Social disadvantage and ethnicity were found to impact the likelihood of very high HbA1c levels and thus increase the likelihood of cardiovascular risks (James et al., 2012). It is important to raise the significance of improving glycaemic control in the younger population as they carry forward their habits into older age. Although some of the GPs concerns regarding QOF targets may be valid, evidence suggests that a large part of the variation in treatment outcomes for patients with T2D is related to the provided care (Heald et al., 2018).

7.3.1.1.2 Diet and exercise

In the qualitative interviews the GPs briefly mentioned they would treat patients with diet and exercise before initiating pharmacological treatment. In the quantitative study 60% of the respondents reported that they would always or often offer their patients diet and exercise *before* or *along with* initiating pharmacological treatment. The NDA showed that in 2018-19 88.3% had their Body Mass Index (BMI) check which is an improvement as compared to previous years (NHS Digital, 2020a). Further, 65% of patients in England and Wales who were diagnosed in 2015 were offered structured education within one year of diagnosis. However, the NDA data also shows that in the same year only about 7% patients attended a structured education programme. It is estimated that there is an underestimation of

attendance due to poor recording. A UK-based study conducted by Maguire et al. found that over half of the patients initiated on oral treatment were clinically obese. They reported that these findings suggested that the patients had not achieved the desired benefit of lifestyle interventions (Maguire et al., 2014). Another study conducted in England and Wales during the same time period reported that 88% of patients had a BMI ≥25 kg/m^2 within three years prior to receiving their first drug treatment (Datta-Nemdharry et al., 2017). In a health survey conducted in England it was reported that 25% of the adult population had a BMI≥25 kg/m^2 in 2013 and hence were overweight (NHS digital, 2013). In study 1 it was demonstrated that most of the GPs did not have a comprehensive understanding of patient education programmes. One study conducted in the hospital setting found that 56% of trainee doctors wanted further training in educating patients with diabetes (George et al., 2008). The second Diabetes Attitudes, Wishes and Needs (DAWN2) study found that 62% of the UK respondents found that healthcare professionals needed more tools to help people at risk of diabetes loose weight (Holt et al., 2013).

7.3.1.1.3 First-line treatment

The majority of the respondents in the quantitative study preferred metformin (97.7%) at treatment initiation for patients with T2D. This is accordance with the qualitative study where all participants reported to prescribe metformin for their patients when comorbidities/ contraindications/patient preferences were not an issue. The high percentage of healthcare professionals who used metformin at treatment initiation is in line with current treatment guidelines in England (NICE, 2015) and international guidelines (Davies et al., 2018; SIGN, 2017). Walley et al. conducted the first study which documented the prescribing trends in England (Walley, Hughes, & Kendall, 2005). The study found that rise in metformin prescribing corresponds to the publication of the landmark study, the United Kingdom Prospective Diabetes Study (UKPDS) (UKPDS, 1998c). This study found that early addition of metformin with sulfonylurea improved HbA1c significantly over a three year period. While the introduction of national guidance (NICE, 2002) in 2002 reinforced metformin as first-line treatment the guidance did not alter the upward prescribing trend. Other studies on prescribing trends using varying UK primary care data showed metformin to be prescribed as first-line treatment in between 84.4% to 91% of prescriptions (Datta-Nemdharry et al., 2017; Filion et al., 2009; Maguire et al., 2014; Overbeek et al., 2017; Sharma et al., 2016; Walley et al., 2005; Wilkinson et al., 2018). Similarly to the trends in the UK, the systematic literature review (chapter 2) found that the global trends between 2000 and 2017 showed an increase in the use of metformin and decrease in the use of sulfonylurea during treatment initiation (Ramzan et al., 2019b).

7.3.1.1.4 Second-line treatment

The self-reported preferred choices at first treatment intensification were SGLT-2i (41.6%) followed by DDP-4i (21.6%) and sulfonylurea (20.8%). This is in accordance with the flexible NICE guidance (NICE, 2015) on the use of add-on combination therapy when initial drug treatment with metformin has not continued to control HbA1c to below the person's individually agreed threshold for intensification.

Sharma et al. found that in 2013 sulfonylurea and DDP-4i accounted for 61.7% and 26.9% of combination therapies with metformin, respectively (Sharma et al., 2016). Similarly, a multi-national study showed that 45% of patients in the UK were prescribed sulfonylurea as combination therapy with metformin (Overbeek et al., 2017). Another study showed that DDP-4i were most commonly (42%) prescribed as second-line treatment in 2016 (Curtis et al., 2018). Wilkinson et al. reported that in 2017 DDP-4i and SGLT-2i accounted for 42% and 22% of add-on therapy, respectively (Wilkinson et al., 2018). Likewise, Dennis et al. reported that the use of DDP-4i as second-line treatment had increased from 22% to 41% between 2010 and 2017(Dennis et al., 2019). In accordance with the findings from the systematic literature review (chapter 2) the qualitative study confirmed that the use of sulfonylurea has been decreasing and other treatments such as DDP-4i and SGLT-2i are increasingly used as second-line treatment.

7.3.1.1.5 Third-line and fourth line treatment

The self-reported preferred choices at second treatment intensification were SGLT-2i (27.2%), GLP-1RA (25.6%) and DDP-4i (19.2%). As with the first stage of intensification this is also in accordance with the flexible NICE guidance (NICE, 2015). The literature reported that 28% patients were treated with DDP-4i as mono- or combination therapy as third-line treatment (Overbeek et al., 2017). Further, twenty nine percent (29%) patients were treated with DDP-4i as monotherapy or in combination as fourth line therapy (Overbeek et al., 2017). Dennis et al. reported that SGLT-2i were prescribed as third-line drug class in 28% patients in 2017 (Dennis et al., 2019). GLP-1RA were reported to largely be reserved for third and fourth line treatment (Curtis et al., 2018).

7.3.1.2 Prescribing practices by drug class

In this section, the reported use and indications of each antidiabetic drug class will be discussed in context of NICE prescribing recommendations and relevant evidence.

7.3.1.2.1 Metformin prescribing trends

In study 2, the use of metformin was self-reported as the most preferred treatment during treatment initiation. Similar views were shared in study 1, where the interviewees additionally added that metformin was their preferred drug of choice if it was not contraindicated. These prescribing trends are in accordance with national and international prescribing guidelines (Davies et al., 2018; NICE, 2015; SIGN, 2017). An advantage of metformin therapy is weight stability or weight loss as compared to other antidiabetic drug classes. Additionally, metformin may also reduce the risk of cardiovascular disease outcomes (Ferrannini & DeFronzo, 2015; Griffin, Leaver, & Irving, 2017). In a study conducted by Heintjes et al. it was reported that patients who received metformin in any treatment combination were more likely to have a high Body Mass Index (BMI) but less likely to use cardiac drugs or have renal complications (Heintjes et al., 2017). These findings are consistent with the licensed product use as the product information label for metformin advises to use the drug with caution in patients with severe renal failure (GFR <30 ml/min), acute metabolic acidosis, heart failure, and use with caution in elderly

(Electronic medicines compendium, 2020). A study conducted in the UK found that 15%-18% of patients experienced an increase in their HbA1c levels after initial non-insulin antidiabetic medicine treatment (Maguire et al., 2014).

7.3.1.2.2 Sulfonylurea prescribing trends

In study 2, it was shown that sulfonylurea was the most common alternative to metformin as first-line treatment although only mentioned by a very small percentage of respondents. This was also reflected in the interviews with the GPs in study 1. This is in accordance with current prescribing guidelines (NICE, 2015). Heintjes et al. reported that patients receiving sulfonylureas in combination with any other drug class, were using cardiac drugs, were of older age, were less likely to have high BMI and had increased risk of renal complication (Heintjes et al., 2017). In study 1, it was reported that sulfonylurea were preferred when it was desired to achieve rapid therapeutic response. This was in line with NG28 which recommends the use of sulfonylurea for this very reason (NICE, 2015). Some GPs (study 1) mentioned concerns about using sulfonylurea due to the possibility of inducing hypoglycaemia. This is in accordance with previous findings from clinical practice which suggest that despite treatment with sulfonylurea being inexpensive, it is often not sustainable to maintain glycaemic control due to added risk of hypoglycaemia and weight gain (Sola et al., 2015). Sulfonylurea was the third most common self-reported preference as second-line treatment. A study conducted by Cook et al. found that patients prescribed metformin and sulfonylurea remained on the combination therapy despite having HbA1c levels ≥8.0% (Cook, Girman, Stein, Alexander, & Holman, 2005). This indicates that there is a resistance to add a third agent even though it is clinically appropriate to do so.

7.3.1.2.3 Thiazolidinediones prescribing trends

The qualitative interviews indicated that the use of thiazolidinediones has been decreasing over the last ten years. These finding are in line with antidiabetic medicines prescribing trends reported in chapter 2. Non-specific concerns about the use of thiazolidinediones still seems to be a concern among the interviewed GPs. This could indicate that the GPs are aware of the association of thiazolidinediones with heart failure (Nesto et al., 2004) and fractures (Kahn et al., 2006). In 2007, a meta-analysis conducted by Nissen et al. (Nissen & Wolski, 2007) reviewed 42 clinical trials and found statistically significant increase in the risk of myocardial infarction and non-significant increase in cardiovascular deaths in patients treated with rosiglitazone. Interestingly, a retrospective study (Hall, Smith, Curtis, & McMahon, 2011) on changes in thiazolidinediones prescribing trends following the rosiglitazone warning (EMA, 2007) showed that although the meta-analysis by Nissen er al. only reported on clinical trials from rosiglitazone there was observed a peak in the switch of both rosiglitazone and pioglitazone. The switch patterns were found to be non-predictable as they were not related to cardiovascular disease, and the authors concluded that the switch simply could be due to non-specific safety concerns. Evidence from the literature in other therapeutic areas shows that the response to license restrictions can vary. One study on antipsychotic prescribing found that when the license of thioridazine was changed and no clear guidance was given on alternative treatments prescribers in Scotland and

England adapted different prescribing behaviour (Bateman et al., 2003). In England the prescribing of thioridazine was replaced by risperidone, chlorpromazine and olanzapine while in Scotland it was mainly replaced by chlorpromazine. Similarly, when the analgesic co-proxamol was removed from the UK market there was a rapid increase in prescribing of other analgesics treatments (Hawton et al., 2009).

7.3.1.2.4 Dipeptidyl peptidase-4 inhibitors prescribing trends

Study 2 showed that DDP-4i was the second most commonly preferred treatment as first treatment intensification. This observation is different from the time trends described in recently published primary care database studies (Curtis et al., 2018; Dennis et al., 2019; Sharma et al., 2016; Wilkinson et al., 2018). The discrepancy between the findings in study 2 and database studies can possibly be explained by two reasons; First the prescribing choices described in study 2 are a reflection of the respondents' personal preferences, and hence do not necessarily reflect their own prescribing in clinical practice. During the interviews with GPs, and the feedback sessions with the practice pharmacists, it was shared that they would be prompted about which antidiabetic medicines to prescribe, and hence their prescription would not necessarily be a reflection of their prescribing preference. Secondly, the high self-reported preference towards use of SGLT-2i could also be an indicator that most of the respondents are experienced antidiabetic medicines prescribers.

7.3.1.2.5 Insulin prescribing trends

Practices for initiating insulin in primary and secondary care varied between GPs (study 1). Hence insulin prescribing practices were explored further in study 2 where the analysis demonstrated that about half of the respondents' initiated insulin in primary care. In the qualitative interviews (study 1), the use of insulin was often associated with more severe disease, and the initiation of insulin was often introduced to therapy regimen after unsuccessfully controlling disease with other treatments. A previous study on trainee doctors found that only 27% were confident managing intravenous insulin (George et al., 2011). Cook et al. found the mean HbA1c to be 9.9% when patients were first prescribed insulin (Cook et al., 2005). In a study covering primary care prescribing from 2000 to 2012 the authors found that 12% were prescribed insulin as their first ever prescription with a mean HbA1c of 9.89% (Datta-Nemdharry et al., 2017). Patients who received insulin as add-on to metformin had a mean HbA1c of 10.03% (over a 90-day period). The study further found that 75% of insulin users received this as second treatment intensification.

In the quantitative survey (study 2) it was shown that the majority of the respondents would initiate the patient on insulin monotherapy. According to NG28, if the patient is symptomatically hyperglycaemic, clinicians are recommended to consider treatment with insulin or sulfonylurea, and review treatment once glucose control has been achieved (NICE, 2015). Alternatively, the advice is to prescribe insulin as last-line therapy when HbA1c is ≥7.5% and the patient has been prescribed three antidiabetic treatments. The current evidence on the impact of early insulin for patients with T2D is limited. The

UKPDS compared intensive glycaemic control (treated with metformin or insulin therapy) versus conventional glycaemic control and found that the patients treated with intensive glycaemic control had reduced microvascular and macrovascular complications (Holman et al., 2008; UKPDS, 1998a). Further, it has been found that early insulin initiation in newly diagnosed patients improve and preserve beta-cell function (Weng et al., 2008). Outcome Reduction With Initial Glargine Intervention (ORIGIN) compared insulin glargine versus standard treatment and found that insulin glargine had neutral cardiovascular outcomes (Gerstein et al., 2012). Additionally, it was shown that patients on insulin glargine had increased hypoglycaemic events and induced a small weight gain.

7.3.1.2.6 Glucagon-like peptide 1 receptor agonists prescribing trends

In the qualitative study the knowledge and training to use of GLP-1RA varied between GPs. Further, the quantitative study found GLP-1RA treatment was self-reported preference as third-line treatment among 25% of the respondents. Primary care prescribing data showed that the use of GLP-1RA was largely reserved as third-line treatment (Curtis et al., 2018). This trend reflects the flexibility of current NICE guidance (NICE, 2015) as the drug class is indicated for use in patients with BMI above 35 kg/m^2 when triple therapy is not effective, not tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a GLP-1RA. In the qualitative study early use of GLP-1RA was often rationalised by referring to the NICE statement that early use of GLP-1RA was indicated when *'weight loss would benefit other significant obesity-related comorbidities'* (NICE, 2015).

As described in the results of study 1, some GPs said that they prescribe GLP-1Ra earlier than recommended in the NICE guidance. Additionally, the local guidance on the use of GLP-1RA was reported to vary and local consultants recommended use of expensive GLP-1RA instead of the cheaper ones due to better efficacy. Several head-to-head studies which compared the clinical efficacy of GLP-1RA have shown that there are differences in the potency for HbA1c reduction and weight loss (Witkowski et al., 2018). Retrospective analysis of pharmacy dispensing data showed that after the first year of treatment about 25% of patients on GLP-1RA are switched to another treatment (Divino, Boye, Lebrec, DeKoven, & Norrbacka, 2019; Divino et al., 2017). Some of these patients were switched to another GLP-1RA while most of them are switched to another drug class. Of note, although several studies have compared the available GLP-1RA there is scarce understanding of the effect of switching between these treatments. The evidence on prescription trends on the use of GLP-1RA are constantly evolving reflecting the publication of clinical trial outcomes. It is fundamental for the positioning of GLP-1RA in the treatment regimen that clinician have a good understanding of the drug class' safety profile and ability to reduce HbA1c, body weight benefits as well as systolic blood pressure in conjunction with heterogenous patient characteristics (Almandoz, Lingvay, Morales, & Campos, 2020).

7.3.1.2.7 Sodium-glucose co-transporter 2 inhibitors prescribing trends

In the qualitative interviews, the use of SGLT-2i was mainly described by experienced GPs while less experienced GPs wanted more information on how and when to use the drug class. Current NICE

guidance on use of SGLT-2 is vague; in the treatment algorithm (*see figure 1.3*) a footnote clarifies the recommendations for use of SGLT-2i as combination and triple therapy. Further, in the main guidance document, clinicians are referred to a HTA on NICE's guidance on canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes (NICE, 2016). The recommendations from SIGN and ADA-EADS consensus report (Davies et al., 2018; SIGN, 2017) are more prescriptive as they tell prescribers which drug to choose under varying clinical circumstances whereas the guidance from NICE gives suggestions and leaves the final choice to the prescriber. Diabetes experts in the UK seem to be aware about the conflicting messages and opinions about efficacy, safety and positioning of SGLT-2i and as an attempt to support decisions making in clinical practice, they have formed an expert panel under the name 'The Improving Diabetes Steering Committee' (Wilding et al., 2018a). The panel has published a review with key evidence from clinical trials and its implications for clinical practice. The review is intended as a tool which can support clinicians in identifying people most likely to benefit from treatment with SGLT-2i. Currently the review has 32 citations in the literature. The usefulness of consensus statements in clinical practice are discussed in section 7.3.2.1.4.

It is notable that about 42% of the respondents in study 2 chose SGLT-2i as their preferred second-line treatment. As discussed above this observation varies from the trends described in literature (Dennis et al., 2019; Wilkinson et al., 2018). In comparison to the UK, sulfonylurea is still the most commonly prescribed second-line treatment in the United States (Montvida, Shaw, Atherton, Stringer, & Paul, 2018). This indicates that there has been a much quicker uptake of DDP-4i and SGLT-2 inhibitors in the UK. One study reviewed primary care data in England from 128 practices in order to compare the use of SGLT-2i with the NICE guidance (McGovern, Hinton, & Lusignan, 2017). The study found that NICE guidance was not being followed. Nine hundred and fifty-six patients (57.5%) were found to be treated with SGLT-2i using combinations not recommended by NICE.

Finally, it is worth mentioning that the less experienced GPs hesitance in using SGLT-2i may be influenced by the Medicines and Healthcare products Regulatory Agency (MHRA) safety advice on the increased risk of lower-limb amputations associated with the use of canagliflozin (MHRA, 2017). Furthermore, the MHRA also advised clinicians to be aware of the increased risk of diabetic ketoacidosis when using SGLT-2i (MRHA, 2016).

7.3.1.3 Cost of antidiabetic medicines

7.3.1.3.1 Cost and antidiabetic medicines prescribing

In the quantitative study (study 2) cost of the drug was indicated a consideration when choosing between drug classes by 25%. When the respondents were asked if they consider the price of the medicine when prescribing for patients with T2D, 50% of the respondents indicated that they did. Furthermore, only 35% of the respondents said they compared the cost of new and old antidiabetic medicines . In the qualitative study it was viewed to be appropriate to consider prescribing older drugs before trying newer treatments as these were considered more expensive. This ethos is similar to previous findings which indicate that cost-conscious consensus creates a mutual expectation that it is important and appropriate to consider cost of medicines when prescribing (Jacoby et al., 2003). Some

GPs expressed that they were hesitant in using newer antidiabetic treatments which were not on the NICE prescribing guideline as they know that drugs not included on the NICE guidance are likely to more costly than alternatives on NICE guidance. This highlights the contrast between the expectation of NICE guidance being appropriately integrated into patient care and NICE providing clear guidance based on the principle that opportunity costs of treatment during prescribing decisions should be minimised (Jacoby et al., 2003). However, the GPs generally reported that the care of the patient was more important than cost. This is similar to previous studies which reported cost of be secondary to effectiveness and safety of the prescribed drugs (Prosser & Walley, 2005).

7.3.1.3.2 Price of GLP-RA treatments versus clinical benefits

In study 3 the cost of one year's treatment maintenance with once-weekly semaglutide 1.0 mg versus once-daily liraglutide 1.2 mg in 27 EU Member States, Norway, Switzerland and United Kingdom was surveyed. The ratio between cost of one-year's treatment with liraglutide versus semaglutide was found to vary between 0.74 and 1.61. As previously mentioned the use of GLP-1RA in Europe is consistent with national guidance and reimbursement systems so the advantage of using one drug as compared to the other would depend on the which rebates the individual company has negotiated with Novo Nordisk (Vogler et al., 2014; Vogler et al., 2015). A European study for instance showed that the uptake of GLP-1RA prescribing was higher in the UK and France as compared to Netherlands, Spain and Italy and suggested that this trend could be explained by differences in national guidelines and reimbursement systems (Overbeek et al., 2017). Besides the cost of treatment, the use of GLP-1RA should also be seen in the context of the clinical benefits. In the Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) 10 trial (Capehorn et al., 2020) it was demonstrated that semaglutide was superior in reducing HbA1c levels, body weight and composite endpoint targets when treating with once-weekly semaglutide 1.0 mg as compared to liraglutide 1.2 mg. When presuming 100% adherence to treatment regimen, despite having a higher acquisition cost, once-weekly semaglutide 1.0 mg is better in terms of long-term treatment cost savings. Additionally, once-weekly semaglutide has also shown significantly greater reduction in HbA1c and weight as compared to other incretin-based therapies (Mishriky, Cummings, Powell, Sewell, & Tanenberg, 2019). However, as other treatments within its group, semaglutide also has increased likelihood of discontinuation of treatment due to GI adverse effects, and hence this should be a consideration when choosing this treatment (Mishriky et al., 2019). In study 1, some GPs mentioned that they use GLP-1RA earlier than indicated in NICE and explained this by the drug class' ability to reduce weight. According to the World Obesity Federation (2015) the proportion of patients who are obese in the UK are among the highest in Europe (World Obesity Federation, 2015) . The BMI statistics showed that 60.2% men and 51.8% women ≥18 years in the UK were obese. In comparison, 54.6% men and 36.1% women ≥18 years in Italy were found to be obese which may also explain the differences in the national guidance in the two countries. One study based on observational studies and meta data has found that GLP-1RA to be safe and effective in clinical practice as observed during clinical trials (Chatterjee, Davies, & Khunti, 2018). However, treatment with newer antidiabetic medicines such as GLP-1RA is expensive as compared to older established generic oral therapies (Stedman et al., 2019). As a measure to contain the

expenditure, NICE recommends discontinuation of treatment if the following criteria are not met; 11 mmol/mol (1%) reduction in HbA1c and weight loss of 3% of initial body weight within 6 months of treatment initiation (NICE, 2015). Further, there is lack of long-term safety data on GLP-1RA as they have only been on the market for a limited period of time.

7.3.2 Objective 2: What are the influences on type 2 diabetes prescribing decisions in primary care?

Objective 2 has been answered using findings from study 1, and hence the influences on T2D prescribing decisions are presented and discussed from a GP perspective. The discussion of the findings has been organised according to macro, micro and meso levels of healthcare.

7.3.2.1 Influences at the macro level: national level

This section discusses macro level influences on GPs beliefs and behaviours about antidiabetic medicines prescribing in primary care.

7.3.2.1.1 Trust in recommendations provided by NICE

Although the GPs did not use NG28 during day-to-day prescribing, the guidance from NICE was described as salient for their prescribing practices as they used secondary information sources which were based on NG28. These findings are similar to previous reports which indicates that NICE guidance in isolation is of little use for GPs when making prescribing decisions (Scoggins, Tiessen, Ling, & Rabinovich, 2007; Wathen & Dean, 2004). Wathen et al. found that when the guidance coincided with personal experiences or other information sources then HTA could increase prescribing of a drug. However, this increase was not always sustained over time (Wathen & Dean, 2004). Further, the GPs questioned the evidence behind some of the drug class choices in NG28 as they were not applicable in primary care and speculated whether these were driven by individuals in the T2D Guideline Development Group (GDG). Previous studies have found that production of clinical guidelines in which the prescribers trust increase adherence to guidance and promote rational prescribing (Owen-Smith et al., 2010; Rashidian et al., 2007). During production of guidelines GDGs use best evidence from primary care patients or lower risk populations. If this is not available, GDGs can adapt high-quality evidence from secondary care. However, this population group is often a high-risk population and may not be a true reflection of the primary care population (Steel et al., 2014). If this is not explicitly acknowledged during the evidence appraisal the guideline is compromised as it may result in patient harm (Lenzer, Hoffman, Furberg, & Ioannidis, 2013; Morris & Ioannidis, 2013). Given that NICE guidance follows a well-established process (NICE, 2020) it is likely that most studies are randomised controlled trials (RCTs) which have been appraised using the Consolidated Standards of Reporting Trials (CONSORT) guidance. Nevertheless, a study on NICE's guideline on Chronic obstructive pulmonary disease (COPD) found that appraised studies used for this guideline only vaguely referred to the setting of the appraised studies (Scullard, Abdelhamid, Steel, & Qureshi, 2011). Additionally, a recent study has shown that patient and public involvement in guideline development influenced the guidelines

development, scope, patient-relevant topics and planes approaches. The study concluded that that patient and public involvement as an important to increase the trustworthiness of the produced guidelines (Armstrong, Mullins, Gronseth, & Gagliardi, 2018).

Turning to the question of whether newer antidiabetic medicines had been given enough emphasis during the production of NG28. The evidence which is selected to be used during developments will always be a matter of debate among experts regardless of therapeutic area. This was also evident during the production of NG28 where a number of opinion pieces were written by diabetes experts on the recommendations in the guideline (Green et al., 2015; Hawkes, 2015; Hillson, 2016; O'Hare et al., 2015a; O'Hare et al., 2015b). Scullard et al. suggested that the uptake of guidance can be increased by involving primary care representatives in the GDGs (Scullard et al., 2011). In study 1, there were varying views on whether primary care GPs could influence NICE guidance. While some GPs found that NICE is not open for communication as opposed to their local CCG, others found them to be visible through their consultation process. Further, the GPs found that they lacked support and motivation to get involved in guideline development. Primary care GPs identified themselves as the frontline of T2D care but found that they are unable to take lead/influence the treatment of patients and this clearly warrants further investigation.

7.3.2.1.2 Remuneration for diabetes care

In the qualitative study the GPs expressed concerns about how the QOF payment scheme can be a barrier to providing quality diabetes care. QOF is a primary care payment-for-performance-scheme and the debate around if funding equals better quality care is not new (Thorne, 2016). The QOF points relate to the diabetes care process which incentivise general practices to undertake certain activities such as keeping a register of adult patients with diabetes, recording a set percentage of patients on their patient list that achieve the recommended targets for blood pressure, cholesterol and HbA1c (glycaemic control). Additionally, a set percentage of those who are newly diagnosed with T2D have to be referred to a structured education programme within 9 months of entry on to the diabetes register (Diabetes UK, 2018). NICE is responsible for recommending changes to QOF and in August 2017 three additional performance indicators were added to the list (NICE, 2017). In the Diabetes, Attitudes, Wishes and Needs (DAWN) study conducted across a number of countries, it was reported that physicians perceived their countries' payment system as a barrier to diabetes care (Peyrot et al., 2006). The level of barriers varied between 26% and 67% with a mean of 54% barriers which showed a statistically significant difference between countries. The study found that primary care physicians and specialist physicians reported similar level of barriers. The follow-up study, DAWN2 study found 24.6% of UK respondents recognises the remuneration system to be a barrier when providing diabetes care (Holt et al., 2013). The mean score for all the surveyed countries was 45%.

GPs for instance found it difficult to deliver good quality care to elderly patients without compromising their own ethical duty of providing treatment that in the patients' best interest. Doran et al. compared general practices from most deprived to least deprived and found that financial incentive schemes may contribute to reduction in inequality in the delivery of care (Doran, Fullwood, Kontopantelis, & Reeves,

2008). Other research suggested that the practices within varying socioeconomic areas score equally in QOF (Dixon et al., 2011). Further, research suggests that patient-centred care has been negatively affected by the introduction of payment for performance incentives (Campbell, McDonald, & Lester, 2008; Maisey et al., 2008). Seen in the context of multimorbidity among patients with chronic conditions evidence shows that quality of care has not improved in therapeutic areas without payment-for-performance incentives and hence this patient group may be disadvantaged if the QOF scheme is not retained in England (Steel, Maisey, Clark, Fleetcroft, & Howe, 2007). Of note, a study which modelled the reduction in mortality across all clinical indicators found that in the first year following the contract, only 11 in 100,000 lives per year were saved. Further, in the second year of the contract most general practices had already exceeded the target payment levels (Fleetcroft et al., 2010).

7.3.2.1.3 Differences in national and international prescribing guidelines

The GPs found that there was contraindicating prescribing recommendations in national and international T2D prescribing guidelines within three areas: glycaemic targets, the choice of drugs and the sequence of drugs. The NICE T2D guidance is directed by attainment of HbA1c target with preference to antidiabetic medicines which has the lowest acquisition cost (NICE, 2015). Choosing treatment based on HbA1c levels sounds sensible in itself however for this approach to result in good treatment outcomes, patients would need to be aware of their HbA1c levels (Trivedi et al., 2017). Research on self-knowledge about HbA1c levels among T2D patients shows that only 50% are aware of their HbA1c levels (Trivedi et al., 2017). Further, the guidance did not recommend routine monitoring of HbA1c which makes this approach unsustainable. Looking at the drug choices and sequence of drugs, the NICE guidance is very flexible and does not offer much prescriptive advice regarding how to choose between drug classes. Further, the first draft guideline published in 2015 did not include much guidance on the use of SGLT-2i as they were relatively new at the time however this was provided later on as described above. The SIGN guidance and ADA–EASD consensus report have been updated more recently and provides concise and prescriptive guidance with user-friendly illustrations of their recommendations (Davies et al., 2018; SIGN, 2017). In the guidance provided by SIGN, the focus has remained on HbA1c control but this has been paired with prescriptive consideration to drug characteristics (SIGN, 2017). ADA–EASD consensus report has moved the focus from glucose control to individualised goals of treatment. This could for instance be reduction of complications coupled with cardiovascular risk management (Davies et al., 2018). Amusingly, diabetes experts have described the relationship between the three clinical guidelines for T2D in the UK as follows: "*If clinical guidelines for T2DM were an edifice, NG28 would be a wall, SIGN 154 would be a room and the ADA–EASD consensus report would be a house"* (Seidu & Khunti, 2019).

7.3.2.1.4 Conflicting messages and opinions

With respect to the GPs knowledge about the recommendations in NG28 the GPs used secondary sources of information as they found NG28 to lacked prescriptive recommendations. The guidance published in 2015 stated "*The wording used in the recommendations in this guideline (for example,*

words such as 'offer' and 'consider') denotes the certainty with which the recommendations is made (the strength of the recommendations)" (NICE, 2015). Without going into semantics and meaning of words, this definition has later been removed during an update of the guidance but the terms are still used. The interviews with the GPs indicate that the rather flexible guidance on how and when to use antidiabetic medicines meant that the individual GPs' choice of antidiabetic medicines instead has been influenced by recommendations in CCG formularies, consultants, hospital prescribing as well as secondary resources based on NG28. Conflicting messages and opinions from various sources seemed to make those less experienced more conservative in their prescribing approach. In the literature it has been suggested that the need for discussion of clinical recommendations arises when there is a lack of comprehensive evidence that does not allow a definite statement to be made (La Brooy, Pratt, & Kelaher, 2020). The lack of definite prescribing guidance from NICE has resulted in higher use of secondary sources which interpret the findings from NICE. Further, as indicated in the literature there is a preference towards certain drug classes in certain areas of England (Curtis et al., 2018; Dennis et al., 2019; Wilkinson et al., 2018). GPs expressed willingness to adapt prescribing of newer treatments even before they were recommended by NICE. While the experienced antidiabetic medicines prescribers expressed that they followed their own experience with treating patients with T2D, less experienced GPs were struggling to differentiate between antidiabetic medicines. A combination of the vague guidance and generalist primary care prescribers need for guidance on use of newer treatments (GLP-1RA and SGLT-2i) may explain the increasing number of consensus statements on T2D prescribing in the literature (Bailey, 2018; Bain et al., 2019a; Bashier et al., 2019; Danne et al., 2017; Inzucchi & Fonseca, 2019; Rutten & Alzaid, 2018; Sattar, 2019; Schernthaner & Schernthaner, 2020; Seidu, Mellbin, Kaiser, & Khunti, 2020). As opposed to clinical guidelines which have been appraised using an appraisal tool such as AGREE and AGREE II (NICE, 2020) expert opinions are ranked as the lowest form of evidence (Evans, 2003). Yet, a number of consensus statement (Bailey, 2018; Bain et al., 2019a; Bashier et al., 2019; Danne et al., 2017; Inzucchi & Fonseca, 2019; Rutten & Alzaid, 2018; Sattar, 2019; Schernthaner & Schernthaner, 2020; Seidu et al., 2020) have been published on positioning of antidiabetic drug classes since May 2019 when NICE announced that guidance on management of adults with type 2 diabetes is due for a review.

7.3.2.2 Influences at the micro level: General practice level

This section discusses micro level influences on GPs beliefs and behaviours about antidiabetic medicines prescribing in primary care.

7.3.2.2.1 Delivery of diabetes care in primary and secondary care

The role of primary care healthcare professionals has evolved to undertake treatment of most patients with T2D. Additionally the support from other healthcare professionals such as nurses and practice pharmacist also varied among the interviewed GPs. Research suggests that patients who have less complex clinical needs can be managed in primary care settings (Campmans-Kuijpers, Baan, Lemmens, & Rutten, 2015; McGill et al., 2016) and patients with multiple morbidities should be referred

to hospital outpatient settings (McGill et al., 2016). With the increasing occurrence of chronic kidney disease in patients with T2D, the inclusion of specialities such as nephrologists and cardiologists have also been found to be useful in multidisciplinary healthcare teams (Riordan, McHugh, Harkins, Marsden, & Kearney, 2018). This is especially pertinent for treatment of complex patients who may benefit from newer antidiabetic treatments which have proven renal benefits (Bain, Cummings, & McKay, 2019b). This approach has been reported to have reduced hospitalisation and cardiovascular events and hence reduced the disease burden on the healthcare system (Nicholson, Cranston, Meeking, & Kar, 2016).

The GPs in the qualitative study described varying professional roles and identities within the healthcare teams. Holt et al. found that optimal treatment outcomes and patient satisfaction delivered by a multidisciplinary healthcare team requires a patient-centred approach which clearly defines the role of the individual team members (Holt et al., 2013). Further, it was reported that it is difficult to keep experienced nurses in primary care once they had been trained. In the DAWN2 study it was reported that 61.3% of the UK respondents found that more qualified nurse-educators or specialist diabetes nurses should be available (Holt et al., 2013). Another study showed 50% of all trainee doctors wanted to learn more about involving doctors, nurses and diabetes specialists during treatment (George et al., 2008). Only one interviewee raised concern about communication within the healthcare teams. In the DAWN2 study found that almost half of the UK respondents (46.1%) wanted better communication within the team (Holt et al., 2013).

Some GPs expressed concerns about involving secondary care in the treatment due to patient-concerns about attending appointments outside the primary care setting. Research investigating patient perspectives of multidisciplinary healthcare team approaches showed that the respondents had concerns about seeing multiple healthcare professionals and attending appointments with multiple healthcare professionals (Berkowitz, Eisenstat, Barnard, & Wexler, 2018). However, the study concluded that that the patients found T2D treatment was better managed by a multidisciplinary healthcare team approach but found co-located teams more convenient when attending appointments.

7.3.2.2.2 Experiences with prescribing antidiabetic medicines

Knowledge about antidiabetic medicines and experiences with prescribing antidiabetic medicines were key influences on prescribing decisions. Similar to previous studies on GPs' prescribing behaviours the interviewees struggled to recall or keep up with changing clinical recommendations (Ab, Denig, van Vliet, & Dekker, 2009; Crosson et al., 2010; Haque, Emerson, Dennison, Navsa, & Levitt, 2005).The most commonly mentioned GP attributes which influenced prescribing decisions was experiences with prescribing antidiabetic medicines. Previous studies have identified clinical experience in any therapeutic areas as contributing factor to prescribing behaviour (Chou et al., 2013; Magzoub et al., 2011; Rajendran, Sajbel, & Hartman, 2012). It was found that clinicians' exposure to different classes of medicines and patient outcomes are expected to increase with clinical experience and years of service. Similar to previous findings (Carthy et al., 2000) on prescribing behaviours, experienced antidiabetic medicines prescribers were described to use head-held formularies. Less experienced antidiabetic medicines prescribers were found prescribe 'standard treatment' and then refer patients

either to another clinician within the practice or to hospital. This study additionally found that experienced antidiabetic medicines prescribers would often take over prescribing of complex patients who needed bespoke treatments. This is in accordance with previous findings which indicates that experienced prescribers use personal and informal medicines lists which may conflict with clinical guidelines (Carthy et al., 2000). Further, a previous study on how doctors choose antidiabetic medicines have reported that diabetes specialists care for patients with longer duration of diabetes, more diabetes comorbidities and more complex medical regimen (Grant et al., 2007).

Noticeably the experience of the only interviewed registrar GP is not very different from the rest of the interviewed cohort of GPs. The registrar GP was mindful that their medical training had not prepared them for prescribing outside what is considered 'standard treatment'. Two studies have looked at T2D prescribing experiences among trainee doctors in the hospital setting. The study by George et al. was undertaken in three UK hospitals and assessed the trainee doctors' confidence, practices and perceived training needs. The study found that 82% of trainee doctors were often, almost always or always confident in identifying cardiovascular risk factor, 68% in identifying foot complications, 74% in diabetic nephropathy and 43% in identifying eye complications (George et al., 2008). Interestingly, 67% reported that would like further training in diagnosing complications of diabetes and 73% in how to modify treatment for diabetes. The second survey was administered in all UK hospitals and asked the trainee doctors about their training in diabetes management (George et al., 2011). The authors found that among trainee doctors only 27% were confident in diagnosing diabetes, 55% were confident diagnosing and managing hypoglycaemia, and 43% were confident managing diabetic ketoacidosis.

7.3.2.2.3 Use of information sources when making prescribing decisions

Due to the complex nature of NG28 treatment algorithm (*see figure 1.3*) the recommendations needed to be translated to be applicable in clinical practice. Similar to previous studies on adherence to clinical guidelines (Owen-Smith et al., 2010; Rashidian et al., 2007; Sheldon et al., 2004; Wathen & Dean, 2004) present study showed that the GPs adapted the guidance to the extent which it was convenient for them. The GPs were interested in prescribing support which was easy to read and adapt in clinical practice. Due to the beliefs about the usefulness of NG28 the GPs adapted information sources which were believed to be based on NICE. These for instance includes local CCG formularies, the BMJ and Hot topics. They were described to be useful due to being user-friendly and providing guidance on how to choose between available treatments. Furthermore, local CCG formularies were appraised for frequently updating their guidelines to include recommendations on when to use newer treatments. Although, this was mainly mentioned when the CCG guidance coincided with the prescribers own prescribing preferences. Of note, a previous study used medical records to investigate the associations between guideline adherence and health outcomes and did not find any clear association between the two variables (Oude Wesselink, Lingsma, Robben, & Mackenbach, 2015).

The decision to use newer treatments was based on a combination of factors related to the GPs confidence, skills and knowledge, dissatisfaction with treatment outcomes from previously prescribed therapy as well as perceived benefits of new antidiabetic treatments. Experienced GPs based their

decision to try newer treatments on evidence from clinical trials and required lower levels of information about the drugs from outside. Other prescribers adapted use of newer treatments once they had seen effective treatment outcomes from treatments initiated by other clinicians. Similar to previous studies on prescribing behaviours the GPs reported that seeing a newer treatment used in secondary care gave it acceptability (Buusman et al., 2007; Jones et al., 2001). Research in other therapeutic areas showed that GPs were influenced by hospital prescribing and/or would follow consultants guidance in their use of newer drugs (Jones et al., 2001). Contrary to studies in other therapeutic areas it was observed that none of the GPs mentioned visits from pharmaceutical representatives (Carthy et al., 2000; Jones et al., 2001) which may indicate a shift in the role and influences of pharmaceutical representatives over time.

7.3.2.2.4 Glycaemic control among patients

Although there was a pushback against the idea of poor control the GPs did identify barriers to achieving good treatment outcomes. It was interesting to hear that they believed that this was the patients' fault due to poor adherence to therapy. None of the GPs suggested that poor adherence could be related to poor treatment choices or lack of skill to choose appropriate treatment. The GPs referred to QOF targets as an indicator that their patients are achieving glycaemic targets. The NDA shows that between 2009 and 2015 about 90% patients with T2D underwent HbA1c monitoring at 6-month intervals as recommended by NICE (NHS Digital, 2020a). However, only 65-67% patients met the NICE treatment target of HbA1c levels of ≤58 mmol/mol, ≤7.5% (NICE, 2015). The poorest treatment outcomes were seen among patients aged over 40 years and those aged between 40 and 64 years (NHS Digital, 2020a).

7.3.2.2.5 Delay in treatment intensification by general practitioners

Most GPs would prescribe metformin monotherapy during treatment initiation. Maguire et al. reported that only 1.8% of patients were prescribed a combination or two oral treatments during treatment initiation (Maguire et al., 2014). One UK study which looked at time to treatment intensification showed that less than 40% of patients on metformin had their treatment intensified within one year of treatment (Watson, Das, Farquhar, Langerman, & Barnett, 2016). Another study found that the median time on first treatment in the UK was 40 months, second-line about 23 months and third-line about 22 months (Overbeek et al., 2017). Comparing these figures with the statistics from NDA may suggest therapeutic inertia when a change in treatment is clinically appropriate. National and international clinical guidelines recommended adding a second treatment when adequate response from a single treatment is not achieved (Davies et al., 2018; NICE, 2015; SIGN, 2017). Further, it has been found that the chances of needing a switch in medicines was almost 2.5 times more likely for each 10 mmol/mol increase in HbA1c level as measured one year after initiation of non-insulin antidiabetic medicines. Prescribing of multiple medicines is associated with reduced adherence to treatment (Claxton, Cramer, & Pierce, 2001; Mateo et al., 2006) and as a result smaller reductions in HbA1c levels (Bain, Feher, Russell-Jones, & Khunti, 2016). A study which has recently been conducted in the US found that up-titrating metformin was as

effective as adding a second-line treatment when looking at glycaemic control after 6 months (Mahabaleshwarkar, Liu, & Mulder, 2019).

GPs were aware about the lag between treatment initiation and the time to first treatment intensification. In the qualitative study a number of clinician and patient-related barriers to optimal treatment outcomes were identified such as clinician or patient concerns about hypoglycaemia, lack in confidence in how to start insulin and nonadherent patient behaviours. Clinical inertia has been described to occur among T2D patients for a long time and is well-described in the literature (Nam, Chesla, Stotts, Kroon, & Janson, 2011; Rushforth, McCrorie, Glidewell, Midgley, & Foy, 2016). Khunti et al. for instance found significant delays in intensification of pharmacological treatment in people with HbA1c ≥7.0% (≥53 mmol/mol), ≥7.5.0% (≥58 mmol/mol), or ≥8.0% (≥64 mmol/mol) the delay before intensification with second treatment was 2.9, 1.9 or 1.6 years, respectively (Khunti et al., 2013). Similar results have been reported in another study (Wilding et al., 2018b). Zafar et al. reported that clinicians in general are willing to accept a degree of responsibility for clinical inertia. However, clinicians lessen their own accountability by highlighting patient and system-related barriers such as comorbidities and time constraints (Zafar, Stone, Davies, & Khunti, 2015). It has been reported that lack of knowledge about recent evidence based guidelines may affect diabetes outcomes, here there was especially emphasis on uncertainty about when to start insulin as well as which and how much should be used (Brown et al., 2002).

The findings from study 1 clearly indicates that patients who may be eligible for newer treatments are not always prescribed these due to reluctance from primary care GPs. Beliefs and behaviours about antidiabetic medicines (*see figure 4.3*) have led to variances in prescribing practices where experienced T2D prescribers described a quicker uptake of newer treatments as compared to less experienced prescribers. A survey on the management of T2D in primary care in Australia found that GPs were less likely to change sulfonylurea as compared to diabetologists (Jiwa et al., 2011). The authors suggested that familiarity with the drug class could be a possible reason for its popularity in primary care. Furthermore, the authors hypothesised that this trend was a reflection of hesitance among clinicians to prescribe newer drugs. In a US-based study Arnold et al. modelled the impact of the use of empagliflozin which was used in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 diabetes Mellitus Patients (EMPA-REG OUTCOME) and liraglutide which was used in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial using patient data from an outpatient registry (Arnold et al., 2017). In this study 26.2% and 48.0% of patients met the eligibility criteria for EMPA-REG OUTCOME and LEADER, respectively. In this study only 6.0% and 5.1% were treated with empagliflozin and liraglutide, respectively. The study concluded that patients who received the treatment or treatment from a similar drug class achieved a lower cardiovascular disease burden as compared to patients who received another treatment. Further, they estimated that 354 cardiovascular deaths and 231 hospitalisations for heart failure could had been prevented with the optimal use empagliflozin (EMPA-REG OUTCOME). Three hundred and twenty nine (329) cardiovascular and 247 myocardial infarctions could had been prevented from optimal use of liraglutide

(LEADER). Similar to Jiwa et al (Jiwa et al., 2011) this study also speculated whether this was due to hesitance from clinician and warranted further investigation necessary.

Study 1 found that both patients and GPs were reluctant initiating insulin as this was perceived a last resort when other antidiabetic treatments had not worked. This has previously been identified as reasons for clinical inertia (Avignon, Attali, Sultan, Ferrat, & Le Breton, 2012). Prescribing of newer treatments such as GLP-1RA was also described as a delay tactic to initiate insulin. In the literature GLP-1RA are described to be used as an alternative to basal insulin or as combination treatment for patients who are already on basal insulin (Meece, 2018). Furler et al. has described barriers and enablers for insulin in general practice (Furler, Spitzer, Young, & Best, 2011). The authors identified three main themes within primary care; varying perceptions of the primary aim of diabetes care, the roles of involved healthcare professionals and the discussion of simplicity and complexity of initiating insulin. The study found that insulin initiation in primary care would require support from nurses and identified this as a key role for nurses and diabetes nurse educators. Although this study was published about 10 years ago optimal insulin initiation still seems to be a challenge in primary care. This is also highlighted in the qualitative study where GPs expressed concerns about not being able to keep experienced nurses in primary care.

7.3.2.2.6 Shared decision-making

The GPs recognised the importance of patient involvement in the consultation and decision-making. However, the GPs found that most patients lacked engagement. This leads us back to the GPs quest for effective strategies to support changes in patient behaviours. The research shows that patients who take part in their treatment decisions achieve better treatment outcomes (Rachmani, Slavachevski, Berla, Frommer-Shapira, & Ravid, 2005; van Dam, van der Horst, van den Borne, Ryckman, & Crebolder, 2003; G. C. Williams et al., 2005). Further, these patients are also found to score clinicians higher for their communication skills in patient satisfaction surveys (Alazri & Neal, 2003; Harris, Luft, Rudy, & Tierney, 1995; Kerr, Smith, Kaplan, & Hayward, 2003; Piette, Schillinger, Potter, & Heisler, 2003). Additionally, it has been found that patient involvement in the decision-making process has influenced clinicians to change their prescribing decisions (Cockburn & Pit, 1997; Macfarlane, Holmes, Macfarlane, & Britten, 1997) and it may be possible that increased engagement from patients would force clinicians to prescribe treatments outside their comfort zone.

Study 1 found that the GPs reported that patients need to take responsibility for management of their condition. DAWN2 found patient self-management capabilities as a barrier to adequate diabetes care (Holt et al., 2013). The GPs talked about a range of emotions when dealing with the patient care. The GPs especially expressed frustration around patient non-compliance to diabetes management plans, patients' fears of injectable treatment and side-effects from the treatment. Further, lack of titration of tablets and insulin, poor concordance with medicines, insulin refusal and side-effects of therapy have previously been identified as barriers in the literature (Khan et al., 2011). GPs reported that they could monitor patient' compliance from their prescribing software but did not report on how they support patients in changing medicine use behaviour. The literature reports that there is an errors perception

that prescribing software can be used to monitor adherence as a prescription refill does not provide information on timing and quantity of medicine intake (Claxton et al., 2001). A more effective measure of compliance is suggested to be electronic monitoring as this technology records the date and time each dose is removed from the electronic monitoring unit (Cramer, Mattson, Prevey, Scheyer, & Ouellette, 1989).

7.3.2.3 Influences at the meso level: Clinical Commissioning Group level

This section discusses meso level influences on GPs beliefs and behaviours about antidiabetic medicines prescribing in primary care.

7.3.2.3.1 Visits from medicines management teams

Most GPs mentioned that the local medicines management team would pay them a visit and influence them to prescribe cost-effectively. It was noted that some descriptions of these visits were detailed while others were somewhat patchy or absent indicating that some GPs had direct visits from the CCG pharmacists while others may only have heard about it through clinical meetings at the practice. It seemed that some GPs lacked understanding of the role the pharmacist played in their practice. The use of visiting pharmacists have been found to improve GP prescribing for more than two decades (Avorn & Soumerai, 1983). After the interviews had been completed Primary care networks (PCNs) were introduced in July 2019 and since then more pharmacists have become involved in primary care treatment within their preferred therapeutic areas (Petty, 2019).

7.3.2.3.2 Comparative prescribing reports on prescribing within general practices in Clinical Commissioning Groups

Most GPs mentioned that their CCG would send them a quarterly evaluation on their prescribing costs. Although none of the interviewees identified themselves as high volume prescribers of antidiabetic medicines the GPs did mention that this would make them compare themselves against other general practices in the CCG. Prosser and Walley who have previously conducted a study on prescribing behaviours among GPs in North West of England found that both low and high cost prescribers found it appropriate to prescribe high cost drugs when cheaper alternatives were not tolerated or has been ineffective (Prosser & Walley, 2003).

7.3.2.3.3 Communication with local hospitals and consultants

GPs frequently communicated with local hospitals and consultants through formal and informal channels. Through referrals the consultants were able to advice on initiation of newer treatments and also on how to continue treatment initiated in the hospital setting. This kind of knowledge is described as *authority knowledge* in the literature and encompasses sharing of knowledge between experts to novices (Ross, 2012). A previous study has found that younger GPs would get inspiration for their prescribing from senior GPs and hospital prescribing (Buusman et al., 2007). Although knowledge

sharing increases the skills of the primary care GPs, Carthy et al. found that consultants were unaware about prescribing cost differences in primary and secondary care (Carthy et al., 2000). Another study emphasised the necessity of continuous monitoring of fundholding and influence of hospital prescribing practices on prescribing in primary care (Weiss et al., 1996). A more recent report published by the King's Fund found that hospitals are responsible for about 50% of the total NHS expenditure on medicines (The King's Fund, 2018). The volume of items prescribed in primary has increased however the overall in expenditure has increased steadily. A cross-sectional study which looked at applicability of national guidelines on blood pressure lowering treatment in primary care found that primary care patients have less severe disease than patients treated in secondary care (Mant, McManus, & Hare, 2006). It was estimated that people with a higher risk of adverse event occurrence usually experience more treatment benefits while the risk of adverse events from treatment remains constant. If empirical evidence based on findings from more severe patients are used on less severe patients the risk of harm potentially outweighs the benefits of the treatment.

7.3.2.3.4 Variation in geographical prescribing and cost of antidiabetic medicines

The GPs reported that the local CCGs provided them with local prescribing formularies to facilitate their prescribing. The GPs generally felt that the local formularies were useful, especially if the formulary included guidance on how and when to use newer treatments. However, the CCGs recommendations for prescribing varied. One GP for instance mentioned to work in two neighbouring CCGs which had different guidelines on which insulin formulation to use during insulin initiation. Other examples of differences in use were medicines from DDP-4i and GLP-1RA. Geographical variation in prescribing of antidiabetic medicines in England have already been identified in previous research and linked to flexible guidance on choice of therapy after metformin in the NG28 (Curtis et al., 2018; Dennis et al., 2019; Wilkinson et al., 2018). However, there was no clear understanding what was driving the variations in the CCGs. The findings from this study are possibly the first one to confirm that the flexibility embedded in the guidance from NICE enables local areas to produce local formularies based on their own interpretation of the scientific evidence and still follow NICE guidance. Other contributors to the observed geographical variations in prescribing includes diversity in need for therapeutic treatment due to differences in practice list size (Milton, Hill-Smith, & Jackson, 2008). Further, patients with multimorbidity such as elderly patients may be treated with multiple medicines (polypharmacy) and may benefit from treatment with newer antidiabetic medicines which are more costly than older treatments. Curtis et al. found that geographical areas in England which used metformin and sulfonylurea as their preferred treatments had lower prescribing cost as compared to those geographical areas which preferred newer treatments (Curtis et al., 2018). Additionally, the study found that the expenditure on antidiabetic medicines over a 12-month period ranged between £60 and £200 across CCGs in England. The study estimated that if all CCGs annually spent according to the lowest decile, which is £95 per patient per year, it would be possible to save £113 million. However, although this may the case it would not reflect the preferences or practices by clinicians in primary care.

7.3.2.3.5 Cost saving interventions

While the GPs in this study generally agreed on cost-effectiveness as a worthy goal for patient care they did not consider it their role to monitor the cost. In study 1 it was reported that DDP-4i were well-liked for being weight neutral and having low risk of hypoglycaemia. However, it was also found that the GPs were resistant towards switching from existing DDP-4i to alogliptin. Interestingly a study conducted more than ten years ago by Prosser and Walley reported that primary care GPs in England are resistant to cost-cutting measures unless the effectiveness of treatment could be maintained (Prosser & Walley, 2005). In the NICE guidance it is stated that when two agents within the same drug class are appropriate, the agent with the lowest acquisition cost should be prescribed (NICE, 2015). In some CCGs a within-class therapy switch of existing DDP-4i to alogliptin were conducted. The aim of this intervention was to optimise cost savings while maintaining care standard among patients. Strain et al. reviewed data from six CCGs which showed no statistically significant or clinically relevant changes in HbA1c levels of patients who had been switched to alogliptin (Strain, McEwan, Howitt, & Meadowcroft, 2019). However, the study was able to conclude that the switch was well-tolerated and 81% of the patients remained on alogliptin six months after the switch. The median saving per patient-month was calculated to be £7.24. Another study was conducted with five CCGs which varied in prescribing volume of DDP-4i (Peter, Unadkat, & Beusnard-Bee, 2019). This study showed that all CCGs achieved cost saving by the switch, but only one CCG reported a substantial cost saving. The concerns GPs' expressed about the overall cost of switching patients to alogliptin when considering the cost of consultation time may be valid. However, using alogliptin for future patients where DDP-4i are clinically suitable may lead to cost savings for the general practices. As to the suitability of interchanging alogliptin with other DDP-4i, one systematic review and meta-analysis was able to conclude that all currently licensed DDP-4i showed similar efficacy and safety (Craddy, Palin, & Johnson, 2014). Additionally, Heald et al. found that those general practices which uses DDP-4i more often had better treatment outcomes among their patients (Heald et al., 2018). The authors suggested that this could be because these general practices are better educated in the use of antidiabetic treatments, and are hence able to provide their patients a better service.

The GPs reported varying recommendations from the local CCGs and consultants on the use of cheaper and more expensive GLP-1RA due to better treatments outcomes. A study on the UK healthcare payer perspective based on the head-to-head SUSTAIN 7 trial showed that semaglutide is a cost-effective option as compared to dulaglutide for patients who are not achieving glycaemic control with metformin (Viljoen et al., 2019). Patients treated with semaglutide 0.5 mg and 1 mg experienced fewer diabetes-related complications due to better glycaemic control. The study concluded that once-weekly semaglutide is expected to improve quality-adjusted life expectancy and reduce the cost per patient as compared to dulaglutide. International studies comparing the long-term cost effectiveness of once-weekly semaglutide and once-daily liraglutide similarly found the treatment with semaglutide to be a cost-saving alternative to liraglutide (Malkin, Russel-Szymczyk, Liidemann, Volke, & Hunt, 2019; Malkin, Russel-Szymczyk, Psota, Hlavinkova, & Hunt, 2019). In respect to these findings the consultants in Northern England may be right in recommending primary care GPs to use newer GLP-1RA as compared to older GLP-RA.

7.3.3 Objective 3: What are the challenges in using antidiabetic medicines in primary care?

In this section findings from study 1 will be used to expand on how the T2D treatment paradigm has changed over time and recommendations for practical implications of this current PhD research will be made.

7.3.3.1 Shift in type 2 diabetes treatment paradigm

The qualitative study did not ask the GPs directly about the goal of therapy. However, based on the described prescribing practices it was confirmed that the use of antidiabetic medicines was varying and often suboptimal. The beliefs and behaviours influencing antidiabetic prescribing practices in primary care (*see figure 4.3 for conceptual model*) suggest that although a wider range of antidiabetic medicines are available GPs have varying experiences with prescribing these medicines. The GPs were aware about the clinical benefits of newer treatments (GLP-1RA and SGLT-2i) and insulin but not all GPs had the necessary knowledge and skills to prescribe medicines from these drug classes. This also means that although NICE has a clear definition of the goal of treatment (*see box 7.*1) some GPs may still be prescribing older antidiabetic medicines when it is clinically appropriate to prescribe newer treatments. Similarly some GPs may be overprescribing newer treatments although it may not be clinically appropriate for the patient.

Box 7.1 Goal of treatment for patients with type 2 diabetes

Treatment goals:

"Treatment is aimed at minimising the risk of long-term microvascular and macrovascular complications by effective blood-glucose control and maintenance of HbA1c at or below the target value set for each individual patient" (NICE, n.d.-c)

Macrovascular complications (cardiovascular disease, strokes and heart failure)

- Risk reduction controlled through control of blood glycaemic levels, pressure and lipid levels

Microvascular complications (damage to eye, kidney and nerves)

- Risk reduction controlled through control of glycaemia and blood pressure

Since the introduction of insulin in 1921 (Fralick & Zinman, 2021) treatment with antidiabetic medicines has come a long way. In the early days of T2D treatment reduction in glycaemic levels was assumed to be beneficial. In the period between 1998 and 2008 the treatment landscape was mainly dominated by metformin and sulfonylurea. Since then, a large number of clinical trials have demonstrated reduction in glycaemic levels but at the same time cardiovascular risks associated with use of antidiabetic medicines started to become a concern. In 2008, the Food and Drug Administration (FDA) (FDA, 2008) and subsequently also European Medicine Agency (EMA) (EMA, 2011) required antidiabetic drugs to show glucose-lowering benefits as well as reduction in cardiovascular complications.

The findings from cardiovascular outcomes trials (CVOTs) have advanced the antidiabetic medicines available to be prescribed in clinical practice. Nevertheless, it has not become easier to choose between available treatments. While some long-established antidiabetic medicines e.g. metformin had shown to lower HbA1c levels as well as microvascular events, it has been reported that use of other long-established antidiabetic medicines such as thiazolidinediones (e.g. rosiglitazone) are associated with increased cardiovascular adverse events (Home et al., 2007; Lago, Singh, & Nesto, 2007; Nissen & Wolski, 2007). In the period 2008 and 2018, nine CVOTs had been reported, thirteen CVOTs were under way and four CVOTs had been terminated (Cefalu et al., 2018). To date, only GLP-RAs (liraglutide, semaglutide, dulaglutide and albiglutide) and SGLT-2 (empagliflozin, canagliflozin, and dapagliflozin) have proven significant reduction in rates of cardiovascular events in patients with T2D (Fitchett et al., 2016; Gerstein et al., 2019; Hernandez et al., 2018; S. P. Marso et al., 2016a; Steven P. Marso et al., 2016b; Neal et al., 2017). When looking at the treatment options from an adherence point of view, it could seem that SGLT-2i are favoured due to the oral administration of this drug class. However, the use of GLP-1RA may not be a concern in patients who are already on insulin or another injectable treatment. Of note, upon completion of the A Heart Disease Study of Semaglutide in Patients With Type 2 Diabetes (SOUL) trial, one can expect further changes in the antidiabetic medicines treatment paradigm as oral semaglutide has shown superior reductions in HbA1c levels and weight as well as cardiovascular benefits during clinical trials (Avgerinos et al., 2020).

7.3.3.2 Recommendations for improving type 2 diabetes care

Drawing from the findings study 1 and existing literature the following section provides recommendations for improvement of T2D management in clinical practice on macro, meso and micro levels (figure 7.1).

From this research, it becomes evident that good glycaemic control is *still* the cornerstone of any T2D treatment strategy. However, the evidence points towards a shift in the aim of treatment. Previously there was focus on 'treating the disease' but with the advances in therapy this mentality has shifted towards 'managing the conditions and preventing future complications'. With the increase in diabetes-related complications, it is eminent that healthcare professionals have the skills and knowledge to prescribe the wide range of licensed antidiabetic medicines available in England.

Healthcare systems all over the world are driven by the desire to improve quality of care while keeping the costs down. In England, the Department of Health published the "Innovation, health and wealth: accelerating adoption and diffusion in the NHS" which sought to support the adoption and diffusion of innovation across the NHS (Department of Health, 2011). In 2014, the Five Year Forward View set the vision for the future NHS (NHS England, 2014). Among other things it was the aim to manage the demand of the healthcare system by focusing on the cost and impact of diabetes care as well as preventing more people from developing T2D. Needless, to say that implementing change is both challenging and complex. Based on the qualitative research and review of existing literature, recommendations which can support future interventions on management of adults with T2D in primary care have been constructed and presented as figure 7.1.

The increasing prevalence of disease, rate of mortality and cardiovascular risk among T2D patients indicates that there is a need to improve management of adults with T2D. With the introduction of newer antidiabetic medicines the knowledge base to prescribe optimally seems to vary between GPs. Although it cannot be expected that all healthcare professionals are diabetes experts, they are required to prescribe safe, effective medicines and support patients in getting best outcomes from their treatment. The prescribing competency framework for all prescribing practitioners in the UK (RPS, 2016) provides an outline what good prescribing looks like. This is also split into ten competencies which the individual can reflect on within a given therapeutic areas. As most professionals are required to reflect on their practice and make continuous professional development records for their annual registration renewal this could be used as support to identify individual practitioners' learning needs.

This research indicates that delay in initiation of pharmacological treatment and treatment intensification is an ongoing challenge in diabetes care. Although GPs are aware of this barrier to optimal treatment and multiple studies in the literature have addressed this issue there is a lack of solutions on how to implement interventions which can overcome both patient- and healthcare-related clinical inertia. The use of clinical guidelines in primary care aims to standardise healthcare and plays an important role in the dissemination of new evidence and recommendations for best practice. Current NICE guidance (NG28) on management of adults with T2D has been criticised for being vague and lack prescriptive guidance on how and when to use antidiabetic medicines. NG28 is currently under consultation, and it can be speculated whether the GDG will be inspired by SIGN and ADA-EADS consensus report and provide prescriptive and user-friendly recommendations on how and when to use available antidiabetic treatments. As to the applicability of NICE guidance in clinical practice, evidence has shown that uptake of guidance which lacks sufficient evidence from the target population can be encouraged by involvement of primary care clinicians. Hence, incentives for non-specialist primary care clinicians to get involved in guideline development could improve the credibility of the produced guidelines.

Given the flexibility in NG28, CCGs have been able to make their own interpretation of recommendations and hence had an enormous impact on antidiabetic medicines prescribing in local areas. The lack of definitive guidance from NICE (macro level) has led to differences in availability of treatments, sequence of prescribing and subsequently also led to varying expenditure on antidiabetic medicines across regions. CCGs plays a vital role in the delivery of care and broader treatment goals based on the clinical needs of the local populations. The NHS financial sustainability report found that all CCGs combined had an overspend of £213 million in 2017-18 (NAO, 2019). Further, this study found that GPs resistance towards cost reducing interventions can be overcome by showing them that the effectiveness of treatment could be maintained. Hence knowledge sharing through publications of practice-based initiatives which have proven effective and ineffective in reducing expenditure on antidiabetic medicines should be encouraged. Further research is needed to investigate differences in the acquisition cost of treatments across healthcare settings.

The increasing pressure on primary care is leading to increased expectations towards primary care clinicians' skills and training. Given the current state of management of adults with T2D and the recognised need to develop the role of primary care in delivering T2D care, further research is needed on the roles and responsibilities of individuals within the healthcare teams, as well as on how to develop more collaboration and support for primary care clinicians. Several initiatives have already been taken to optimise treatment in primary care such as introducing joint practice-based clinics for more complex patients. Further, the establishment of practice-based clinics may also incentivise experienced nurses to stay in primary care.

The availability of newer treatments allows clinicians to select treatments based on the patients' individual circumstances such as weight, obesity, and the risk of cardiovascular disease but this research shows that not all GPs have the necessary skills and training to use these treatments. Subsequently this has led to varying practices and use of antidiabetic medicines in primary care. Further, it is eminent that healthcare professionals communicate effectively with patients and optimise the timing of add on-therapies. Adherence to therapy play a key role in optimal use of antidiabetic medicines and hence it is important to involve them in the decision-making process and address patient concerns before selecting treatment.

The number of antidiabetic medicines available to treat patients with T2D has increased noticeably over the last decade. Additionally, T2D is a complex disease and the use of most antidiabetic medicines are limited by tolerability, efficacy or safety advice. Given that less experienced GPs lack confidence in using newer treatments it is possible that the full range of available treatments are not offered to patients in primary care. Further, the knowledge gained from this research has led the researcher to wonder if current organisational structure makes it possible to prescribe the full range of all available antidiabetic medicines in primary care. From a healthcare system perspective, there are still many unanswered questions as to what yields optimal treatment outcomes. Organisational structures and the use of prescribing guidelines in general practice seems fluid - should prescribing guidelines (macro) drive how clinicians prescribe (micro) or should clinicians' prescribing be driven by their own autonomy or something in between (meso)?

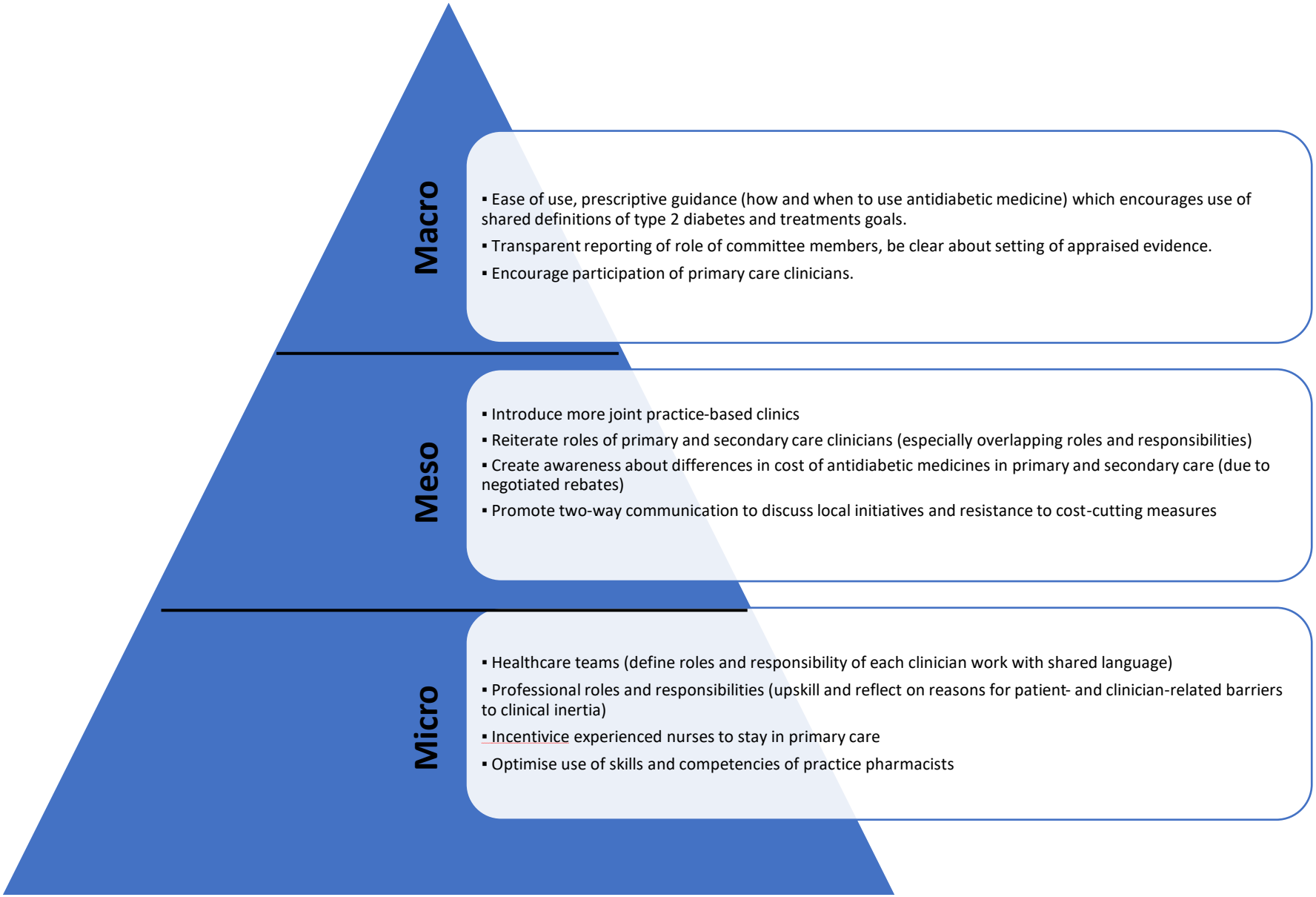


Figure 7.1 Conceptualisation of the recommendations from this PhD thesis for improving treatment outcomes and reducing delay in treatment.

7.4 Strengths and limitations of the mixed-methods study

The findings of the mixed-methods study should be considered in the context of its limitations. In chapter 3 the researcher presented the methodology and methods of this mixed-methods study and in this section the researcher will discuss the strengths and limitations.

7.4.1 Choice of theory

This research was driven by qualitative research and did not use any conceptual framework to drive the inquiry. While using theory to drive research can give more robust results. Lau et al. noted that theory comes in many shapes and it is important to be explicit about the theoretical understanding that underpins the methodology which impacts how data are analysed (Lau & Traulsen, 2017). As stated in chapter 3 using empirical evidence to drive this research fitted well with the philosophy of letting the research drive the research question. Further, this research did not seek to be theory-testing but rather be theory-building. The findings from the qualitative study have led to the development of a conceptual model on beliefs and behaviours influencing antidiabetic prescribing practices in primary care. This can potentially be used by other researchers to build theory-testing research. Further, using a micro, meso and macro sociological framework to provide a deeper data analysis has enabled the researcher to provide recommendations which can support future interventions on management of adults with T2D in primary care. Researchers (and policy makers) can potentially use this list when planning interventions which aims to optimise antidiabetic medicines prescribing practices in England.

7.4.2 Mixed-methods research design

The primary aim of this research was to explore GPs antidiabetic medicines prescribing behaviours in primary care. The secondary aim was to explore what influenced their prescribing decisions in clinical practice. As there was limited literature on the use of NICE guidance when treating patients with T2D it was deemed necessary to start with a broad statement and narrow the topic at later stages of the project. Grant and Dowell described the decision to prescribe new medicines as ‘a multifactorial idiosyncratic’ process (James & Jon, 2002) and by using a qualitative approach it was possible to explore these complex beliefs and behaviours (Pope & Mays, 1995). Due to the vast amount of evidence on management of T2D in the UK, one of the biggest challenges was to choose between ‘relevant’ and ‘not relevant’ literature. Discussions with supervisors and diabetes experts from primary and secondary care were encouraging when important decisions were made, however other researchers may have taken a different direction.

Objective 1, on the use antidiabetic medicines in primary care was answered by triangulating the findings from sub-studies 1-3. The discussion of findings in context of existing literature indicate that there is good reason to believe there is a link between the findings in this mixed-methods study and existing literature. However, as the tool developed in study 2 was not fully validated (discussed further below) objective 2 and 3 were answered using the findings from the qualitative study. The advantage

of having a quantitative study which was based on the qualitative data analysis have been that it helped the researcher to confirm that the challenges identified in relation to diabetes care are still of importance.

7.4.3 Qualitative interviews (study 1)

The qualitative study only sampled GPs and due to the element of self-selection this sample may not fully represent views of other primary care clinicians. It was intended to recruit GPs with varying experience with prescribing antidiabetic medicines for adults with T2D. As the recruitment mainly was conducted using social media and social network those who were interested or motivated were more likely to take part in this kind of research. It was sought to eliminate self-selection bias by encouraging GPs with all levels of experience with antidiabetic medicines prescribing to participate in the study. As the researcher is a community pharmacist this could have introduced researcher bias. The author attempted to reduce the likelihood of bias introducing herself and her background before starting the interviews. As described in the methods (chapter 3) the researcher has sought to be reflective through questioning and exploring her own understanding of the researched field and to ensure trustworthiness through peer debriefing and providing thick description of the research. That being said as described in the researcher's PhD journey in the forewords the researcher had limited prior knowledge about antidiabetic prescribing practices in primary care.

7.4.4 Quantitative study (Study 2)

The reliability coefficient, Cronbach's alpha, was based on a very small sample which questions whether the tool can be considered to be fully validated. As a number of the questions were rephrased or deleted after the pilot study it was intended to retest the survey tool. However, none of the GPs who completed the first pilot questionnaire agreed to participate in the retest of the pilot questionnaire. Given the caveat that participants in any study have the right to withdraw from study or decline an invitation this decision was accepted. The researcher had limited time to conduct the research and as recruitment of another sample of clinicians would require an updated ethical approval from the university it was decided to move ahead without further testing of the tool. This decision was taken after consulting the supervisors and diabetes experts.. As it was aimed to develop a survey tool which was informed by the qualitative study the detailed feedback provided by the GPs was considered more valuable than feedback from another cohort of clinicians. Although the tool is not completely statistically validated their feedback increased the content validity of the developed questionnaire. Further, during the one-to-one sessions the practice pharmacists, who had not seen the questions before, had expressed similar issues/concerns as the GPs had described in their written feedback. If the GPs had agreed to participate in the retest of the pilot questionnaire it would have been possible to statistically validate the tool using a bigger pilot sample.

Although postal questionnaires are known to have low response rates, it was not possible to distribute the survey through email due to lack of access to email addresses. As an attempt to increase the response rate, best practice recommendations to improve response rate were applied such as

addressing the envelopes 'open' so the gatekeeper could share it with any clinician in the general practice. In the reminders the participants who had already taken the survey were encouraged to forward it to another colleague within the practice. Further, practice managers act as gatekeepers who control access to primary care clinicians. Hence participants who might have had an interest in participating in the postal survey may not have received it. It was observed that monetary incentives resulted in to double the response rates (Edwards et al., 2009). However due to limited funding to conduct the PhD research, this was not a feasible option. Using an online survey increased the likelihood of reaching clinicians' whose practice may have received the surveys but not been able to participate due to 'gatekeepers'. The key advantage of this study is that it surveyed primary care clinicians self-reported antidiabetic medicines practices. The practice pharmacist who provided feedback on the pilot questionnaire emphasised that they prescribed drugs which were chosen by the GP or nurse, and for this reason prescribing trends observed in database studies are not necessarily a reflection of the individuals preferred drug choices. This may also explain why the self-reported prescribing choices indicates SGLT-2i as the most common second-line treatment as compared to DDP-4i which were reported in the literature. Another possible explanation would be that most of the respondents were experienced antidiabetic medicines prescribers. It is common for surveys that people are more willing to participate in research in their subject area. In the qualitative study it was established that the number of years in clinical practice did not reflect directly on the experience with regards to using antidiabetic medicines. In hindsight this limitation could had been overcome by asking the respondent to score their level of experience with antidiabetic medicines as the term 'diabetes specialist' is abstract, and according to diabetes experts a self-proclaimed title.

7.4.5 Pricing study (study 3)

This study used ex-factory level reference prices acquired from PPI services. The challenge with using reference prices is that they are not a true indicator of the actual price of the medicines as discounts and rebates are not publicly available (Vogler et al., 2017). However, this is a common issue in pricing surveys. In this context, the price surveys and comparisons are still valuable sources for research and policy decisions (WHO, 2020b). Further, it was sought to adjust for discrepancy in data collection time by correcting for inflation as seen in previously conducted pricing studies (Babar et al., 2019; Iyengar et al., 2016; Vogler, Vitry, & Babar, 2016).

CHAPTER 8

Conclusions and recommendations

8.1 Introduction

The aim of this research was to investigate antidiabetic medicine prescribing practices in primary care. More specifically this research sought to gain in-depth understanding of primary care clinicians' perceptions, knowledge and attitudes regarding prescribing antidiabetic medicines for adults with type 2 diabetes (T2D) and the influence of National Institute for Health and Care Excellence (NICE) prescribing guidance in clinical practice. In order to achieve these objectives a series of studies were conducted to allow general practitioners (GPs), nurses and practice pharmacists to indicate what they considered the role of NICE guidance to be, as well as teasing out varying aspects of how T2D is managed in primary care.

To date, there does not appear to be any published of work following through with understanding the management, prescribing practices and behaviours of clinicians in primary care in England. Many of the findings presented in this thesis have empirical support and coupled with the various data collected on management of adults with T2D it has led to the conclusions of this thesis and proposed implications for clinical practice and future research. This work could be beneficial to aid in the development of future policy and practice decisions related to optimising care of patients with T2D in primary care.

8.2 Thesis conclusions

In this thesis, it was explored how treatment of adults with T2D has changed from focusing on reducing blood glucose levels to a holistic treatment approach which aims to prevent hypoglycaemia and premature cardiovascular mortality. On embarking on this research journey, I asked, which antidiabetic medicines are prescribed during management of adults with type 2 diabetes in primary care? What are the influences on type 2 diabetes prescribing decisions in primary care? What are the challenges in implementing use of newer antidiabetic treatments in clinical practice? Throughout this PhD thesis the research objectives have been answered by exploring three interrelated domains: primary care clinician prescribing behaviours, evolving treatment landscape and the healthcare system in England.

Firstly, this thesis have shown that the management of T2D is complex and current care reflects the combined efforts of GPs, nurses and practice pharmacists in primary care. In addition to providing easy access to care by diagnosing, prescribing and reviewing patients in primary care they also reduce the burden on secondary care. The research have explored how standardisation of care through the implementation of national guidelines have provided the clinician with a shared treatment outcome to work towards. This process has been brought forward by the doctors' medical training, formularies produced by Clinical Commissioning Groups (CCGs) and the QOF. Finally, it was investigated what the influences on primary care GPs' T2D prescribing practices with a focus on who is involved in care of adults with T2D, and what do they know about antidiabetic medicines?

This thesis used an exploratory mixed-methods research design led by a qualitative study to explore GPs' views of management of adults with T2D in primary care. This approach allowed me to draw on multiple methodologies and epistemologies within the same mixed-methods study in order to answer my research questions. By providing varying aspects GPs views of management of adults with T2D this

research have contributed existing knowledge as to how shared understanding of a notions of diabetes care may not necessarily lead to provision of similar care in practice. The burden of disease and diabetes-related complications warrants that clinicians to keep the cost of antidiabetic medicines prescribing down and focus on prevention of T2D. In this thesis challenges at different levels of the healthcare system have been highlighted. This thesis does not embrace all aspects of the management of adults with T2D in primary care. The aim of this research has been to contribute to the field with a nuanced account of multiple effects which could further the understanding of how antidiabetic medicines are prescribed in primary care.

From this mixed-methods study it was learned that GP' prescribing decisions are influenced by their understanding of the patients' condition, the level of immediate risk created by the patients' conditions (e.g. elevation of HbA1c and comorbidities), and their perceived benefit of the available treatments, it was demonstrated that their decision were also influenced by time constraints, training and encouragement to prescribe antidiabetic medicines. Findings from the qualitative study revealed that NG28 was perceived to be complex and onerous which has a substantial effect on the GPs willingness to read this. Subsequently, this led to increased use of local formularies and use of recommendations from consultants which may contribute substantially to the observed geographical variation in antidiabetic medicines prescribing in England.

In conclusion, the management of T2D is complex, and requires a combined effort from multidisciplinary healthcare teams across primary and secondary care. While analysing the practices of primary care GPs the research in this PhD thesis has provided understanding of the challenges in the management of adults with T2D in Northern England. Furthermore, it has highlighted the importance of approaching antidiabetic medicines prescribing, with consideration to the use of older and newer therapies, but also as a practice which shows sensitivity to the prescribing clinician, patients as well as the healthcare system.

8.3 Recommendations

8.3.1 Recommendations for future research

- Further research is required to determine the percentage of patients who are treated according to the licensed indications of the drug classes. This information is available from open prescribing data and could be used to develop evidence based treatment guidelines. Such guideline could also ensure optimal use of the limited healthcare budget. Additionally, this could also resolve the favoring of different drug classes across England.
- The developed quantitative tool is not representative of the population. Nevertheless, it has been useful to further our understanding of organisational structures, preferred antidiabetic drug classes and use of prescribing guidelines. If this tool was refined and tested further it could be used to collect data on national level. Collaboration with diabetes experts with access to gatekeepers would be beneficial.

- As described in the review of literature there is vast of evidence on barriers to effective T2D treatment. This includes clinical inertia around treatment intensification. What is less evident from the literature is that many of the leading diabetes experts reside in the North East and North West of England. Hence, instead of producing consensus statements on how to treat patients with T2D more effort should be made to share knowledge from local interventions. This could for instance be done through creating of a national database where local interventions and experiences could be shared. An example of knowledge sharing could be sharing how waiting times for hospitals have been reduced by using an alternative model where patients are seen by multidisciplinary teams.

8.3.2 Recommendations for policy and practice

- As T2D is mainly managed in primary care it is necessary to train and upskill GPs in the use of newer treatments as well as insulin. It is vital that they are provided training and support in how to communicate effectively with patients about treatment barriers. This could be for instance be done by using the prescribing competency framework for all prescribing practitioners in the UK to identify therapeutic areas where the individuals' knowledge could be upskilled and recorded as a continuous professional development record. Since T2D is related to increased risk of multimorbidity it is important to strengthen local relationship between primary and secondary care. There also need to be a clearer definition of roles and responsibilities of healthcare professionals across the healthcare settings.
- The Royal College of General Practitioners provides guidance on clinical audit in primary care however this study found that there is a lack of ownership of treatment of patients with T2D on a GP level. National introduction of practice-based joint clinics may incentivize experienced nurses to stay in primary care, and subsequently facilitate the lack of support which some GPs experience during their daily practice.
- Since there is a lack of engagement from patients in attending structured education efforts should be made to find a ways to engage patients in diet and lifestyle interventions as the healthcare system cannot sustain the increasing burden from this patient group.
- More effort should be made to be transparent about the dynamics and consensus reached by Guideline Development Groups. The views of all stakeholder including patients should be heard before implementing guidelines as it is vital to increase uptake of guidance. This issue has been raised within other therapeutic areas but until this study was conducted there was only anecdotal evidence on the inconsistent use of the current NICE guidance on treatment of adults with T2D. Despite the intend to include healthcare professionals, patient/public and in the development of NICE guidelines there still seems to be a gap between guideline development and practice. Increased efforts and strategies on involving GPs and patients in the guideline development groups could increase the usefulness of produced guidelines.

- Pharmacists who are working in primary care have various titles such as clinical pharmacist, practice pharmacist and medicine optimisation pharmacist. If skills and training of pharmacists are used optimally, they can play an important role in ensuring safe and effective use of antidiabetic medicines. Since, the qualitative data collection of this research primary care network (PCN) roles have been established, and it would be interesting to see which direction the care of patients with T2D will develop.
- There is also an opportunity for community pharmacists as frontline workers to communicate with patients about their antidiabetic medicines use. Provision of the New Medicines Services in the community pharmacy could support patients in adhering to treatments plans by following up on how they are getting on with their new medicine and if they have concerns about their new medicines.

8.4 Dissemination plans

Table 8.1 Dissemination plan

Proposed title	Journal	Manuscript type	Timeline
Evolution of antidiabetic medicines used in the treatment of type 2 diabetes mellitus over the period 2000-2017: A systematic review of the literature.	Health Services Research & Pharmacy Practice Conference 2018.	Abstract/ poster presentation	Presented
Cost analysis of type 2 diabetes mellitus treatment in economically developed countries.	Pharmacoeconomics Outcomes Research.	Review	Published
Trends in global prescribing of antidiabetic medicines in primary care: A systematic review of literature between 2000-2018	Primary Care Diabetes	Review	Published
Mixed Methods Research in Pharmacy Practice: Basics and Beyond.	Encyclopaedia of Pharmacy Practice and Clinical Pharmacy	Book chapter	Published
Antidiabetics in England: Exploring Prescription Patterns & Health Outcomes.	University of Huddersfield 3-minute thesis competition 2019. *(semi finalist)*	Abstract/ oral presentation	Presented
Is the National Institute for Health and Care Excellence' type 2 diabetes prescribing guidance consistently used among primary care healthcare professionals? A cross-sectional survey in the Northern England.	Diabetes UK Conference 2021	Abstract/ poster presentation	Presented
Once-weekly semaglutide versus once-daily liraglutide: a cross-national price comparison study	Lancet	Original paper	September 2021
A mixed-methods evaluation of antidiabetic medicines prescribing practices in primary care in Northern England	Diabetes, obesity and metabolism	Original paper	September 2021
A qualitative evaluation of influences on antidiabetic medicines prescribing practices in primary care in Northern England	Diabetes, obesity and metabolism	Original paper	October 2021
Management of adults with type 2 diabetes in primary care: what are the challenges in clinical practice?	Primary Care Diabetes	Commentary	October 2021

CHAPTER 9

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Appendices

Appendix 1: PRISMA checklist Trends in global prescribing of antidiabetic medicines in primary care

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	2.3.2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Published paper.
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Chapter 1. Published paper.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2.3.2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2.2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2.3.2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2.3.2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2.3.2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2.3.2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	2.3.2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	2.3.2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	2.3.2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	2.3.2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	2.3.2.4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	2.3.3.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	2.3.3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	2.3.3.2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	2.3.3.2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	2.3.3
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	2.3.5
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and **implications for future research.**	2.3.4+2.5
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Forewords

Appendix 2: PRISMA checklist Cost of antidiabetic medicines

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	2.4.1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Published paper.
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Chapter 1. Published paper.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2.4.1
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2.1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2.4.2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2.4.2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2.4.2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2.4.2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	2.4.2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	2.4.2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	2.4.2.4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	2.4.2.6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	2.4.2.4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	2.4.3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	2.4.3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	2.4.2.4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	2.4.2.4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	2.4.4
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	2.4.5
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and **implications for future research.**	2.4.4+2.5
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Forewords

Appendix 3: Original currencies and examples of calculations

Mean annual direct cost

Country	price year	mean annual direct cost	currency	Number of periods	Inflation	mean annual direct costin 2017 mo	Exchange rate	Currency	mean annual direct cost in 2017 money ($)
UAE, 2010	2004	1,605	$	13	0.02	2076.238642	1	$	2076.238642
Brazil , 2011	2005	1,355	$	12	0.02	1718.467632	1	$	1718.467632
Brazil, 2014	2017	1,012	$	8	0.02	1185.719294	1	$	1185.719294
Davari, 2016	2011	156	$	6	0.02	175.4561049	1	$	175.4561049
Italy, 2017	2012	3,312	€	7	0.02	3803.895562	1.998	€	7,600.18
Lithuana, 2014	2011	448.34	€	6	0.02	504.9036591	1.998	€	1,008.80
Argentina, 2014	2011	3,668.60	AR$	6	0.02	4131.439451	0.0537	AR$	221.86
Germany, 2017	2015	0	€	2	0.02	0	1.998	€	0.00
Iran, 2011	2009	842.6	$	8	0.02	987.2401944	1	$	987.2401944
Spain, 2016	2010	3110.1	€	7	0.02	3572.527295	1.998	€	7,137.91
Singapore, 2015	2010	2,034.60	$	7	0.02	2337.115859	1	$	2337.115859
Germany, 2016	2011	3352	€	6	0.02	3774.896429	1.998	€	7,542.24

Shows how to calculate future value from year x value to year y value.
Future $value = C * (1 + R)^n$

1) UAE future value: 1,605 $ *(1+0.02)^13 = 2076.23 $

2) Nothern Italy future value = 3,312 € * (1 + 0.02)^7 = 3803.89 €

Note down the chosen exchange rate, last day of the year (31/12/2017): 1.998

Mean value 2018 in $: 3803.89 € * 1.998 = 7,600.18 $

Mean annual cost of medicine

Country	price year	mean annual direct cost	currency	Number of	Inflation	mean annual direct in 2017 money	Exchange rate	Currency	mean annual cost of medicine in 2017 money ($)
UAE, 2010	2004	0	$	13	0.02	0	1	$	0
Brazil , 2011	2005	249	$	12	0.02	315.7922068	1	$	315.7922068
Brazil, 2014	2017	113	$	8	0.02	132.3975101	1	$	132.3975101
Davari, 2016	2011	67.8	$	6	0.02	76.35381203	1	$	76.35381203
Italy, 2017	2012	874.07	€	7	0.02	1004.031682	1.998	€	2006.0553
Lithuana, 2014	2011	178.52	€	6	0.02	201.0425151	1.998	€	401.6829451
Argentina, 2014	2011	2,653.55	AR$	6	0.02	2988.328288	0.0537	AR$	160.473229
Germany, 2017	2015	498	€	2	0.02	518.1192	1.998	€	1035.202162
Iran, 2011	2009	200.6	$	8	0.02	235.0348718	1	$	235.0348718
Spain, 2016	2010	925	€	7	0.02	1062.534243	1.998	€	2122.943417
Singapore, 2015	2010	162.1	$	7	0.02	186.2019467	1	$	186.2019467
Germany, 2016	2011	960	€	6	0.02	1081.115922	1.998	€	2160.069613

Appendix 4: 32-item consolidated criteria for reporting qualitative studies (COREQ)

No. Item	Guide questions/ description	Reported in Section/remarks, Page No.
Domain 1: Research team and reflexivity		
Personal Characteristics		
1. Interviewer/facilitator	Which author/s conducted the interview or focus group?	3.2.1.7
2. Credentials	What were the researcher's credentials? *E.g. PhD, MD*	Forewords
3. Occupation	What was their occupation at the time of the study?	Forewords
4. Gender	Was the researcher male or female?	Forewords
5. Experience and training	What experience or training did the researcher have?	Forewords
Relationship with participants		
6. Relationship established	Was a relationship established prior to study commencement?	No.
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.*g. personal goals, reasons for doing the research*	3.2.1.2
8. Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. *Bias, assumptions, reasons and interests in the research topic*	Forewords 3.2.1.2
Domain 2: study design		
Theoretical framework		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? *e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis*	3.1.1 3.2.1.9
Participant selection		
10. Sampling	How were participants selected? *e.g. purposive, convenience, consecutive, snowball*	3.2.1.4
11. Method of approach	How were participants approached? e.*g. face-to-face, telephone, mail, email*	3.2.1.4
12. Sample size	How many participants were in the study?	3.2.1.5 4.3

No. Item	Guide questions/ description	Reported in Section/remarks, Page No.
13. Non-participation	How many people refused to participate or dropped out? Reasons?	3.2.1.6
Setting		
14. Setting of data collection	Where was the data collected? e.*g. home, clinic, workplace*	3.2.1.7
15. Presence of non-participation	Was anyone else present besides the participants and researchers?	3.2.1.7
16. Description of sample	What are the important characteristics of the sample? *e.g. demographic data, date*	4.3.1
Data collection		
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	3.2.1.2
18. Repeat interviews	Were repeat interviews carried out? If yes, how many?	No.
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	3.2.1.8
20. Field notes	Were field notes made during and/or after the interview or focus group?	3.2.1.5; 3.2.1.9; 3.1.1.10
21. Duration	What was the duration of the interviews or focus group?	4.3.1
Data saturation	Was data saturation discussed?	3.2.1.5
Transcripts returned	Were transcripts returned to participants for comment and/or correction?	3.2.1.10; 3.2.2.6
Domain 3: analysis and findings		
Data analysis		
24. Number of data coders	How many data coders coded the data?	3.2.1.9
25. Descrition of the codinpg tree	Did authors provide a description of the coding tree?	3.2.1.9
26. Derivation of themes	Were themes identified in advance or derived from the data?	3.2.1.9
27. Software	What software, if applicable, was used to manage the data?	3.2.1.8

No. Item	Guide questions/ description	Reported in Section/remarks, Page No.
28. Participant checking	Did participants provide feedback on the findings?	3.2.1.10; 3.2.2.6
Reporting		
29. Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.*g. participant number*	4.3
30. Data and findings consistent	Was there consistency between the data presented and the findings?	4.3
31. Clarity of major themes	Were major themes clearly presented in the findings?	4.3.1
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	4.3; 4.3.8

Appendix 5: Hands-on guide to questionnaire research

Item	Section(s)
What information did the researchers seek to obtain?	3.2.2.6
Was a questionnaire the most appropriate method and if not, what design might have been more appropriate?	Focus groups.
Were there any existing measures (questionnaires) that the researchers could have used? If so, why was a new one developed and was this justified?	3.2.2.6
Were the views of consumers sought about the design, distribution, and administration of the questionnaire?	3.2.2.6
Validity and reliability	
What claims for validity have been made, and are they justified? (In other words, what evidence is there that the instrument measures what it sets out to measure?)	3.2.2.11; 7.4.4
What claims for reliability have been made, and are they justified? (In other words, what evidence is there that the instrument provides stable responses over time and between researchers?)	3.2.2.11; 7.4.4
Format	
Was the title of the questionnaire appropriate and if not, what were its limitations?	3.2.2
What format did the questionnaire take, and were open and closed questions used appropriately?	3.2.2.6
Were easy, non-threatening questions placed at the beginning of the measure and sensitive ones near the end?	3.2.2.6
Was the questionnaire kept as brief as the study allowed?	3.2.2.6
Did the questions make sense, and could the participants in the sample understand them? Were any questions ambiguous or overly complicated?	3.2.2.6
Instructions	
Did the questionnaire contain adequate instructions for completion—e.g. example answers, or an explanation of whether a ticked or written response was required?	3.2.2.2; 3.2.2.6
Were participants told how to return the questionnaire once completed?	3.2.2.2; 3.2.2.8
Did the questionnaire contain an explanation of the research, a summary of what would happen to the data, and a thank you message?	3.2.2.6; appendix 9+10
Piloting	
Was the questionnaire adequately piloted in terms of the method and means of administration, on people who were representative of the study population?	3.2.2.6
How was the piloting exercise undertaken—what details are given?	3.2.2.6
In what ways was the definitive instrument changed as a result of piloting?	3.2.2.6+3.2.2.7
Sampling	
What was the sampling frame for the definitive study and was it sufficiently large and representative?	3.2.2.3+3.2.2.4
Was the instrument suitable for all participants and potential participants? In particular, did it take account of the likely range of physical/mental/cognitive abilities, language/literacy, understanding of numbers/scaling, and perceived threat of questions or questioner?	N/A
Distribution, administration and response	
How was the questionnaire distributed?	3.2.2.8
How was the questionnaire administered?	3.2.2.3
Were the response rates reported fully, including details of participants who were unsuitable for the research or refused to take part?	3.2.2.5
Have any potential response biases been discussed?	7.4.4
Coding and analysis	

What sort of analysis was carried out and was this appropriate? (e.g. correct statistical tests for quantitative answers, qualitative analysis for open ended questions)	3.2.2.10+7.4.4
What measures were in place to maintain the accuracy of the data, and were these adequate?	3.2.2.9
Is there any evidence of data dredging—that is, analyses that were not hypothesis driven?	7.2
Results	
What were the results and were all relevant data reported?	5.2
Are quantitative results definitive (significant), and are relevant non-significant results also reported?	5.2
Have qualitative results been adequately interpreted (e.g. using an explicit theoretical framework), and have any quotes been properly justified and contextualised?	N/A
Conclusions and discussion	
What do the results mean and have the researchers drawn an appropriate link between the data and their conclusions?	5.3+7.2
Have the findings been placed within the wider body of knowledge in the field (e.g. via a comprehensive literature review), and are any recommendations justified?	3.1.3+7.2

Appendix 6: SIREC Ethical approval 1 (study 1)

REF: SAS-SREIC-16.11-18-1

University of HUDDERSFIELD
Inspiring tomorrow's professionals

School of Applied Sciences
University of Huddersfield
Queensgate
Huddersfield
HD1 3DH

16th November 2018

Prof Zaheer Babar
School of Applied Sciences
University of Huddersfield

Dear Zaheer,

Re: Ethical Approval of projects entitled: General practitioners' opinions on prescribing diabetes medicines in England: a mixed methods study

Thank you for submitting your proposals to the School Research Integrity and Ethics Committee (SRIEC). I am happy to confirm that the project has been approved from the date of this letter up to and including the 31st July 2019 as indicated on the documents submitted.

We note that your application form states that approval from the NHS is required and that you will apply once you have approval from the Schools ethics committee. This is fine but we want to make it clear that our approval does not allow you to contact participants now but that you have to have approval from the NHS bodies before the study can commence. If this process incurs a significant delay and you need to extend the project end date, please contact me and I will make the changes.

If for any reason the nature of the project changes such that new ethical issues arise, it is incumbent upon you to inform the committee of these changes. In such circumstances, further approval from the committee will be required before any changes to the project are implemented.

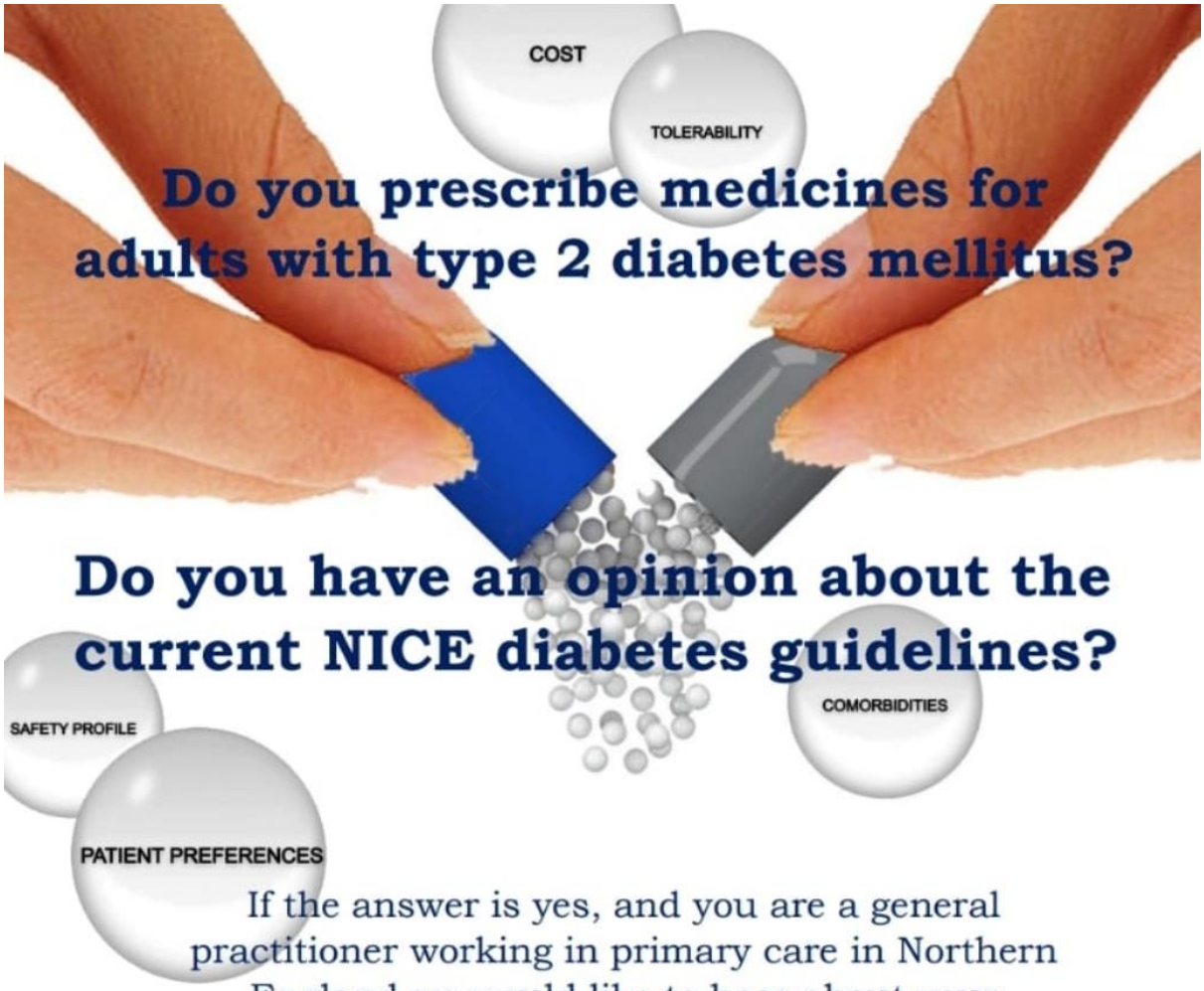
Please quote reference number SAS-SRIEC-1611-18-1 in any future correspondence.

Yours sincerely

R. M. Phillips.

Professor Roger M Phillips BSc, PhD, SFHEA
Chair – School of Applied Sciences Research Integrity and Ethics Committee

Appendix 7: Flyer for social media



If the answer is yes, and you are a general practitioner working in primary care in Northern England we would like to hear about your opinions.

As part of an important study at the University of Huddersfield, we are asking practising general practitioners about their opinions on diabetes prescribing. The study is part of a PhD research project aiming to evaluate how physicians in the UK make choices about treatment of adults with type 2 diabetes mellitus. Your contribution will enable us to understand and explain the usefulness of current prescribing guidelines.

Your opinions will remain anonymous and we will reimburse you for your time.

If you think you would like to take part, please contact lead investigator, Sara Ramzan on **sara.ramzan@hud.ac.uk** or via mobile on [redacted]

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Centre for Pharmaceutical Policy and Practice Research

Appendix 8: Letter of invitation (study 1)

General practitioners' opinions on prescribing diabetes medicines in England: a mixed methods study

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LETTER OF INVITATION

Dear Dr,

We would like your help with a research study. A PhD student at University of Huddersfield is doing a research study about general practitioners' opinions on diabetes prescribing. We are doing this because very little is known about how general practitioners in the UK make choices about treatment of adults with type 2 diabetes mellitus. The enclosed leaflet tells you more about the study.

If you decide to take part in the study a researcher will get in touch with you to arrange for an interview at a place and time convenient to you. The amount of time this would take is small. Your opinions will remain anonymous and you will receive a gift voucher as a token of out appreciation for taking part in the study.

Please read the enclosed information leaflet carefully. If you wish to take part contact Sara Ramzan on sara.ramzan@hud.ac.uk or via mobile on [redacted]

Thanks for your help

Sincerely

Sara Ramzan

Today's date

General practitioners' opinions on prescribing diabetes medicines in England: a mixed methods study

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PARTICIPANT INFORMATION SHEET

What is the study about?

We know that the number of prescription items issued for patients suffering with diabetes has increased by 80 % during the last ten years. We want to make sure these patients are offered the best suitable treatment and care. To do this, we want to know about general practitioners' opinions on how external factors such as NICE guidelines and the price of the prescribed medicine influence their prescribing.

Who is carrying out the study?

This study is being carried out as a part of Sara Ramzan's PhD which is supervised by Prof Zaheer-Ud-Din Babar and Dr Peter Timmins. All members of the research team are bound by the ethical and data protection commitments explained on this form.

Why I have been approached?

You are currently registered as general practitioner and working or have recently worked in a primary care setting in Northern England.

Do I have to take part?

Participation in this study is entirely voluntary. If you decide to take part you will be asked to sign a consent form, and you will be free to withdraw from the study at any stage without giving an explanation to the researcher.

What will I need to do?

If you agree to participate in the study, a researcher will interview you about your opinions regrading medicines being prescribed to treat patients with Type 2 Diabetes Mellitus (T2DM) and your views and perceptions regarding the role of NICE guidelines within the health care system. We would expect the whole interview process to take between 40-60 minutes. The interview will be audio-recorded, with your consent.

Will my identity be disclosed?

All information which is disclosed will be strictly confidential and anonymised in compliance with the Data Protection Act and ethical research guidelines and principles.

What will happen to the information?

All the collected information will be stored securely and accessed only by the researcher and supervisors. Any identifying information, such personal names and general practices, will be removed in order to ensure anonymity. It is anticipated that the findings will be published in the researchers PhD dissertation, journal articles and/or presented at conferences.

Who can I contact for further information?

If you require any further information about the research, please contact reseracher Sara Ramzan on: sara.ramzan@hud.ac.uk or telephone [redacted]

What if I have concerns about this research?

This research has been reviewed and approved by the University of Huddersfield Ethics Committee. If you are worried about this research, or if you are concerned about how it is being conducted, you can contact the Professor Roger Phillips, Associate Dean (Research) and Chair of SRIEC at r.m.phillips@hud.ac.uk.

Appendix 10: Final interview guide

Semi-structured interview guide: General practitioners' opinions on prescribing diabetes medicines in England: a mixed methods study

Version D

Section A – Demographics

- Name
- Age
- Gender
- Years of experience in GP surgery
- Local CCG

Section B - GPs perception on management of adults with type 2 diabetes in the England

1. In general, do you support the current treatment guidelines for management of adults with type 2 diabetes and why?

Which guidelines are you aware off?

2. If and how has the treatment guidelines for management of adults with type 2 diabetes guidance changed in the past few years?
3. The current notion is that adults with type 2 diabetes are inadequately controlled. What is your opinion?
4. Do you find the NICE guidance useful when prescribing medicines?

When would you normally start (straight away or after 3months?)

4.1 What medication do you usually commence newly diagnosed patient with?
4.2 Can you mention an example when you add on a second-line treatment?
4.3 Can you mention an example of when you would prescribe insulin?

How do you decide when to change the treatment of a patient?

How often do you push doses to maximum before adding on second-line treatment?

5. Are there examples of medicines you would like to see recommended by NICE?

Section C – Views and perception regarding the role of NICE in management of adults with type 2 diabetes

1. What is your understanding of the value of NICE in the healthcare system in England?
2. How does NICE influence prescribing of medicines for adults with type 2 diabetes?

Do they restrict you in your prescribing?

3. What are your views on communication between NICE and GPs?
4. How do you voice concerns to NICE?
5. Do the NICE recommendations have sufficient representation from health professional and patients groups?
6. How do you find the decision-making process undertaken by NICE?

Section D – Views and perceptions regarding the role of GPs when prescribing medicines for management of adults with type 2 diabetes in England

1. What is your understanding of general practitioner's role in the treatment of patients suffering from T2DM?
2. What role do you as a GP play in determining which medicines to prescribe for adults with type 2 diabetes?
3. How important is it to involve patient in decision-making for good treatment outcomes? Why?
4. Which role does the NICE recommendations play to achieve desired treatment outcomes?
5. How does the NICE recommendations influence your prescribing?
6. How does the local CCG/ practice management influence your prescribing?

Section E – Views and perception regarding the cost of medicines

1. What is your thought on balancing the cost of medicines versus success in controlling patient outcomes?
2. Do you monitor expenditure on medicines you prescribe for adults with type 2 diabetes compared to other prescribers in your practice?
3. If so, how?
4. Where do you get information about the price of the medicines that you prescribe from? (BNF, NICE, evidence-based literature)?

Appendix 11: Informed consent form

General practitioners' opinions on prescribing diabetes medicines in England: a mixed methods study

INTERVIEW CONSENT FORM

The interview will take between 30-40 minutes. We don't anticipate that there are any risks associated with your participation, but you have the right to stop the interview or withdraw from the research at any time. Thank you for agreeing to be interviewed as part of the above research project. Please read the accompanying ***information sheet*** and then sign this form to certify that you approve the following:

☐	The interview will be audio-recorded and a transcript will be produced
☐	Access to the interview transcript will be limited to Sara Ramzan and academic colleagues and researchers with whom collaboration maybe needed.
☐	Any summary interview content, or direct quotations from the interview, that are made available through academic publication or other academic outlets will be anonymized so that you cannot be identified. Care will be taken to ensure that other information in the interview that could identify yourself is not revealed
☐	Any variation of the conditions above will only occur with your further explicit approval

Quotation Agreement:

I also understand that my words may be quoted directly. With regards to being quoted:

☐	I ***agree*** to be quoted directly if my name is not published and a made-up name (pseudonym) is used.
☐	I ***do not agree*** to be quoted directly even if my name is not published and a made-up name (pseudonym) is used.

By signing this form I agree that;

1. I am voluntarily taking part in this project. I understand that I don't have to take part, and I can stop the interview at any time;
2. The transcribed interview or extracts from it may be used as described above;
3. I have read the Information sheet;
4. I can request a copy of the transcript of my interview and may make edits I feel necessary to ensure the effectiveness of any agreement made about confidentiality;
5. I have been able to ask any questions I might have, and I understand that I am free to contact the researcher with any questions I may have in the future.

_____

Participants printed Name

_____ _____

Participants Signature **Date**

_____ _____

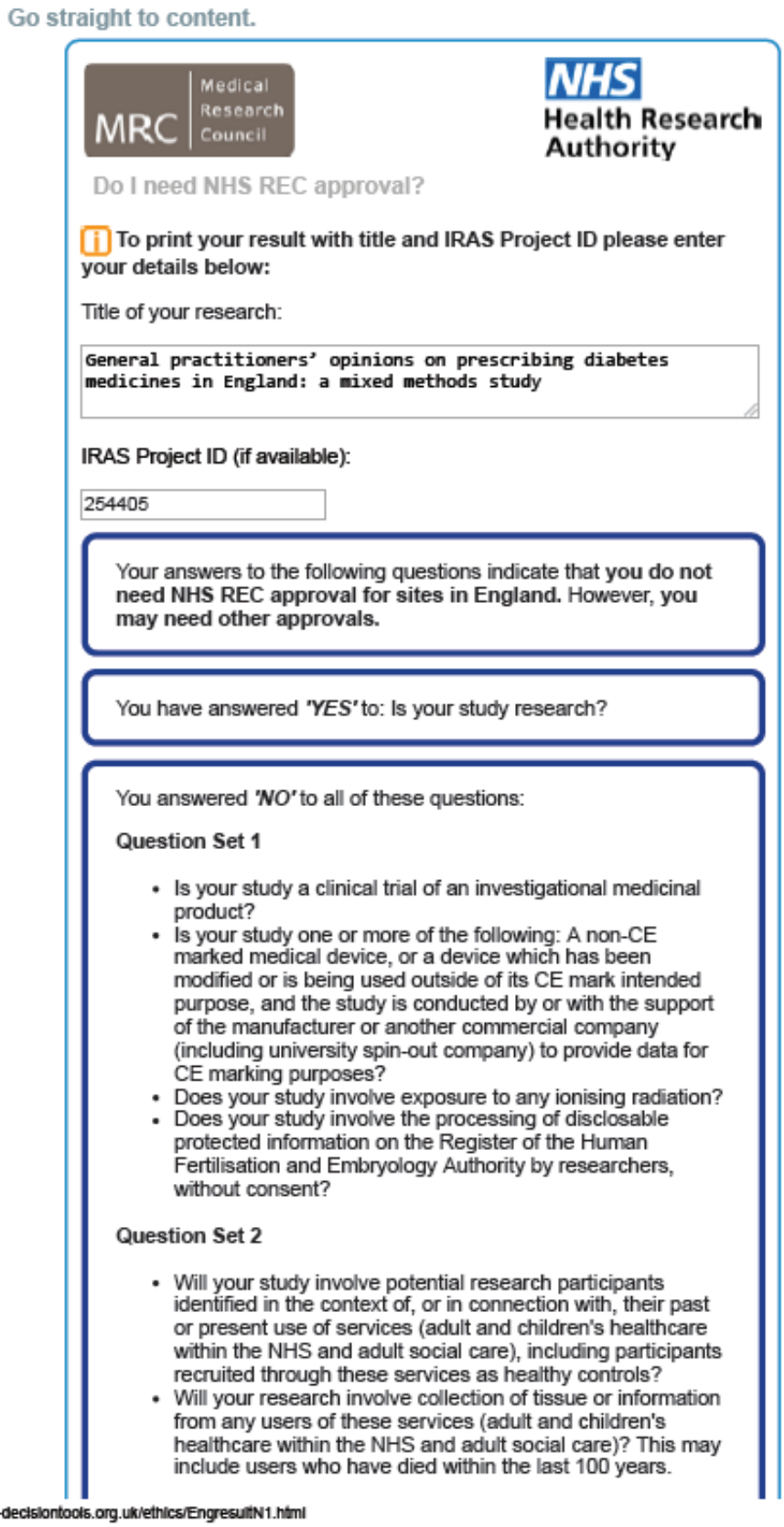
Researchers Signature **Date**

Contact Information

If you have any further questions or concerns about this study, please contact:

Name of researcher: *Sara Ramzan* Institution: *University of Huddersfield, Deparment of Pharmacy* Telephone[redacted] E-mail: sara.ramzan@hud.ac.uk	Name of researcher: *Zaheer-Ud-Din Babar* Institution: *University of Huddersfield, Deparment of Pharmacy* Telephone:[redacted] E-mail: z.babar@hud.ac.uk

Appendix 12: Decision from the Research Ethics Committee



Go straight to content.

MRC Medical Research Council

NHS Health Research Authority

Do I need NHS REC approval?

To print your result with title and IRAS Project ID please enter your details below:

Title of your research:

General practitioners' opinions on prescribing diabetes medicines in England: a mixed methods study

IRAS Project ID (if available):

254405

Your answers to the following questions indicate that **you do not need NHS REC approval for sites in England.** However, **you may need other approvals.**

You have answered ***'YES'*** to: Is your study research?

You answered ***'NO'*** to all of these questions:

Question Set 1

- Is your study a clinical trial of an investigational medicinal product?
- Is your study one or more of the following: A non-CE marked medical device, or a device which has been modified or is being used outside of its CE mark intended purpose, and the study is conducted by or with the support of the manufacturer or another commercial company (including university spin-out company) to provide data for CE marking purposes?
- Does your study involve exposure to any ionising radiation?
- Does your study involve the processing of disclosable protected information on the Register of the Human Fertilisation and Embryology Authority by researchers, without consent?

Question Set 2

- Will your study involve potential research participants identified in the context of, or in connection with, their past or present use of services (adult and children's healthcare within the NHS and adult social care), including participants recruited through these services as healthy controls?
- Will your research involve collection of tissue or information from any users of these services (adult and children's healthcare within the NHS and adult social care)? This may include users who have died within the last 100 years.

http://www.hra-decisiontools.org.uk/ethics/EngresultN1.html

- Will your research involve the use of previously collected tissue or information from which the research team could identify individual past or present users of these services (adult and children's healthcare within the NHS and adult social care), either directly from that tissue or information, or from its combination with other tissue or information likely to come into their possession?
- Will your research involve potential research participants identified because of their status as relatives or carers of past or present users of these services (adult and children's healthcare within the NHS and adult social care)?

Question Set 3

- Will your research involve the storage of relevant material from the living or deceased on premises in the UK, but not Scotland, without an appropriate licence from the Human Tissue Authority (HTA)? This includes storage of imported material.
- Will your research involve storage or use of relevant material from the living, collected on or after 1st September 2006, and the research is not within the terms of consent from the donors, and the research does not come under another NHS REC approval?
- Will your research involve the analysis of DNA from bodily material, collected on or after 1st September 2006, and this analysis is not within the terms of consent for research from the donor? And/or: Will your research involve the analysis of DNA from materials that do not contain cells (for example: serum or processed bodily fluids such as plasma and semen) and this analysis is not within the terms of consent for research from the donor?

Question Set 4

- Will your research involve at any stage intrusive procedures with adults who lack capacity to consent for themselves, including participants retained in study following the loss of capacity?
- Is your research health-related and involving prisoners?
- Does your research involve xenotransplantation?
- Is your research a social care project funded by the Department of Health and Social Care (England)?

If your research extends beyond **England** find out if you need NHS REC approval by selecting the *'OTHER UK COUNTRIES'* button below.

OTHER UK COUNTRIES

If, after visiting all relevant UK countries, this decision tool suggests that you do not require NHS REC approval follow this link for final confirmation and further information.

Print This Page

NOTE: If using Internet Explorer please use browser print function.

About this tool Feedback Contact Glossary

Appendix 13: HRA approval not required

IRAS 254405 HRA Approval not required

Getting too much email? Unsubscribe

HO, Joanna (HEALTH RESEARCH AUTHORITY) <joanna.ho@nhs.net>
Mon 12/31/2018 10:44 AM
To: Sara Ramzan (Researcher)
Cc: Zaheer Babar; Liz Towns-Andrews

Dear Sara

Thank you for your response and updated documentation.

I think there was some initial misunderstanding when we spoke on the phone. Following your email response below and another separate email, it is my understanding that you are intending to contact the GP Practices directly after sourcing this data from the internet as you *'we have used NHS digital website and applied the filter called "NHS England North"'* (which was initially understood as NHS Digital, the organisation when we spoke). You have also confirmed that there is no involvement from the CCGs, so there is no direct NHS involvement in your study.

After assessing your study objective again, it is my understanding that your research involves NHS employees as participants solely by virtue of their professional capacity rather than in relation to their employment by a specific NHS organisation. Therefore, HRA Approval will not be required for your project; I will proceed to withdraw your application.

Please note: following your response to the below queries and more specific in relation to the use of data and the GDPR. I would recommend that you liaise with your academic supervisor/sponsor contact to discuss local policies
[redacted]ts on the use and storage of data before you proceed with your project. You have stated that the study data will not use personal data, however, you will be *processing* personal data as part of your study (ie –
details will be stored and used for the purpose of the research) and it is this use of the data that you must be transparent about in order to comply with GDPR.

[redacted] your study.

Kind regards

Joanna
[redacted]
Assessor

Health Research Authority

NHSBT centre | Holland Drive | Newcastle upon Tyne | NE2 4NQ
T. 020 7104 8005
E. Joanna.Ho@nhs.net
W. www.hra.nhs.uk

Appendix 14: Clinical Commissioning Groups as per NHS July 2018

1 NHS Airedale, Wharfedale and Craven CCG
2 NHS Barnsley CCG
3 NHS Bassetlaw CCG
4 NHS Blackburn with Darwen CCG
5 NHS Blackpool CCG
6 NHS Bolton CCG
7 NHS Bradford City CCG
8 NHS Bradford Districts CCG
9 NHS Bury CCG
10 NHS Calderdale CCG
11 NHS Central Manchester CCG
12 NHS Chorley and South Ribble CCG
13 NHS Cumbria CCG
14 NHS Darlington CCG
15 NHS Doncaster CCG
16 NHS Durham Dales, Easington and Sedgefield CCG
17 NHS East Lancashire CCG
18 NHS East Riding of Yorkshire CCG
19 NHS Eastern Cheshire CCG
20 NHS Fylde and Wyre CCG
21 NHS Greater Huddersfield CCG
22 NHS Greater Preston CCG
23 NHS Halton CCG
24 NHS Hambleton, Richmondshire and Whitby CCG
25 NHS Harrogate and Rural District CCG
26 NHS Hartlepool and Stockton-on-Tees CCG
27 NHS Heywood, Middleton and Rochdale CCG
28 NHS Hull CCG
29 NHS Knowsley CCG
30 NHS Lancashire North CCG
31 NHS Leeds North CCG
32 NHS Leeds South and East CCG
33 NHS Leeds West CCG
34 NHS Liverpool CCG
35 NHS Newcastle and Gateshead CCG
36 NHS North Durham CCG
37 NHS North East Lincolnshire CCG
38 NHS North Kirklees CCG
39 NHS North Lincolnshire CCG
40 NHS North Manchester CCG
41 NHS North Tyneside CCG
42 NHS Northumberland CCG
43 NHS Oldham CCG
44 NHS Rotherham CCG
45 NHS Salford CCG
46 NHS Scarborough and Ryedale CCG

47 NHS Sheffield CCG
48 NHS South Cheshire CCG
49 NHS South Manchester CCG
50 NHS South Sefton CCG
51 NHS South Tees CCG
52 NHS South Tyneside CCG
53 NHS Southport and Formby CCG
54 NHS St Helens CCG
55 NHS Stockport CCG
56 NHS Sunderland CCG
57 NHS Tameside and Glossop CCG
58 NHS Trafford CCG
59 NHS Vale of York CCG
60 NHS Vale Royal CCG
61 NHS Wakefield CCG
62 NHS Warrington CCG
63 NHS West Cheshire CCG
64 NHS West Lancashire CCG
65 NHS Wigan Borough CCG
66 NHS Wirral CCG

List retrieved in July 2018

https://www.england.nhs.uk/north-west/ccgs-and-trusts/ccgs/

https://www.england.nhs.uk/north-east-yorkshire/ccgs-and-trusts/ccgs/

Appendix 15: Receipt of gift card acknowledgement

Date:_____

Project:__ *General practitioners' opinions on prescribing diabetes medicines in England: a mixed methods study*_____

This is to certify that I, _____, received an

Name of Participant

Amazon gift card from this study_____*on NICE diabetes guidelines*_____ in the amount

Research Study

of £_*100*_ on this date _____.

Amount Date Received

Study Participant Signature: _____

Principal Investigator: _____

Card Number: _____

Appendix 16: SIREC Ethical approval 2 (study 2)

REF: SAS-SREIC-25.10.19-1

University of HUDDERSFIELD
Inspiring tomorrow's professionals

School of Applied Sciences
University of Huddersfield
Queensgate
Huddersfield
HD1 3DH

25th October 2019

Prof Zaheer Babar and Sara Ramzan
School of Applied Sciences
University of Huddersfield

Dear Zaheer,

Re: Ethical Approval of projects entitled: General practitioners' opinions on prescribing diabetes medicines in England: a mixed methods study

Thank you for submitting an update to your ethics approval for this study and I am happy to confirm that the project has been approved from the date of this letter up to and including the 31st January 2020 as indicated on the documents submitted. As indicated in your email of 24th October 2019, the following changes/comments were made to the documentation submitted and responses to the points raised in my initial letter of 16th November 2018:

- Ethical approval extended to 31/-01-2020.
- The second phase of the study includes GPs, nurses and pharmacists (initial approval was only for GPs)
- The second phase of the study includes an online survey using Qualtrics (University approved software) as data collection tool (initial approval was only for the postal survey)
- IRAS approval was not necessary as the healthcare professionals are participating in a personal capacity on not on behalf of NHS (we got this in writing)

If for any reason the nature of the project changes such that new ethical issues arise, it is incumbent upon you to inform the committee of these changes. In such circumstances, further approval from the committee will be required before any changes to the project are implemented.

Please quote the following reference number in any subsequent correspondence: SAS-SREIC-25.10.19-1

Good luck with your studies

Yours sincerely

R. M. Phillips.

Professor Roger M Phillips BSc, PhD, SFHEA
Chair – School of Applied Sciences Research Integrity and Ethics Committee

University of HUDDERSFIELD
Inspiring tomorrow's professionals

Centre for Pharmaceutical Policy and Practice Research

Survey on healthcare professionals' Type 2 diabetes prescribing practices

Since the first guidance on the management of adults with Type 2 diabetes mellitus (T2DM) was published by NICE in 2002 new evidence and drug classes have been introduced. Further, an increasing number of healthcare professionals are involved in the treatment of these patients. In this study we are asking healthcare professionals about T2DM prescribing in their general practice. **Any information you provide will remain anonymous and strictly confidential.**

Despite the availability of various prescribing guidelines for management of adults with T2DM; equal access, effective selection and utilisation of medicines may still be a problem. Your contribution will enable us to understand and explain the usefulness of current prescribing guidelines.

The survey should take **about 20 minutes** to complete. Please answer the questions to the best of your knowledge. We **do not** expect you to look at any diabetes prescribing guidelines prior to filling out this survey.

This survey is intended for **all healthcare professionals in the practice** who are involved in the care of adults with T2DM. If you work in practices based in different Clinical Commissioning Groups (CCG), please provide the name of the CCG **where you received this survey** and fill out this questionnaire based on your experience from this practice. Please send your completed survey **using the freepost envelope** provided by **date.**

If you have questions about this survey, or **require more copies of the questionnaire** please do not hesitate to contact the lead researcher, Sara Ramzan, at sara.ramzan@hud.ac.uk.

Please note: By completing this questionnaire you will be deemed to have given your consent to participate in this study

Appendix 18: Pilot questionnaire

Section A | About yourself

Sex			Age (years)					Qualification(s) and year of qualification(s)	Authorised to prescribe		Name of your local CCG
Female	Male	Prefer not to say	<30	31-40	41-50	51-60	>60		Yes	No	

Section B | About your practice

1. ***Which healthcare professionals at your practice are involved in the care of patients with T2DM?*** *- Please tick all that are applicable*

☐ General practitioner	☐ Practice nurse
☐ Diabetes specialist nurse	☐ Pharmacist

Please respond to all the following statements as appropriate

		Yes	No	Unsure
2.	Does your practice have an ***in-house diabetes care team*** treating patients with specific or difficult problems?			
3.	Does your practice refer patients with specific or difficult problems to an ***external diabetes care team*** e.g. secondary care			

Section C | Type 2 diabetes in adults: management (NG28)

		Yes	No	Unsure
4.	Have you consulted the NICE guidance [NG28] ***in order to prescribe*** in the past two weeks?			
5.	Have you consulted any other guidelines/ summaries such as your local CCG formulary ***in order to prescribe*** in the past two weeks?			
6.	Do you feel confident prescribing medicines for adults with T2DM based on current guidance provided by NICE?			
7.	Do you find that the NICE 2015 treatment guidelines [NG28] was up-to-date with evidence ***at the time of publication?***			
8.	Do you find that the NICE 2015 treatment guidelines [NG28] is up-to-date with ***current evidence*****?**			
9.	The range of drug classes recommended by NICE in the NG28 guideline are adequate to treat patients with T2DM in my daily practice			
10.	NICE has taken longer to update current guidance on management of adults with T2DM compared to my local CCG			

How strongly do you agree/ disagree with following statements - *Please tick as appropriate:*

	Strongly agree	Agree	Undecided/ Neutral	Disagree	Strongly Disagree
11. NICE is effective in managing the budget for medicines and achieves the widest possible range of medicines from the available funds					
12. There are adequate opportunities for primary care healthcare professionals to make their concerns known to NICE					
13. There is an adequate number of primary care representatives on the NICE committees					

Section D | Clinical management of adults with T2DM

	Always	Often	Sometimes	Rarely	Never
14. Does your practice educate patients about diet and exercise when first diagnosed with T2DM?					
15. When a patient is first diagnosed with T2DM do you offer diet and exercise as an intervention ***before*** initiating pharmacological treatment?					
16. When a patient is first diagnosed with T2DM do you offer diet and exercise ***along with*** pharmacological treatment?					

17. What is your preferred drug of choice at ***treatment initiation*** if comorbidities/ contraindications/patient preferences are not an issue? **-** *Please indicate **one drug** of choice:*	
☐ Metformin	☐ Sulfonylurea
☐ Thiazolidinediones	☐ SGLT-2
☐ GLP-1	☐ Insulin
☐ DDP-4 (gliptins)	☐ Insulin only
☐ Other	

18. What is your preferred drug of choice at ***first treatment intensification*** if comorbidities/ contraindications/patient preferences are not an issue? **-** *Please indicate **one drug** of choice:*	
☐ Metformin	☐ Sulfonylurea
☐ Thiazolidinediones	☐ SGLT-2
☐ GLP-1	☐ Insulin
☐ DDP-4 (gliptins)	☐ Insulin only
☐ Other	

19. What is your preferred drug of choice at ***second treatment intensification*** if comorbidities/ contraindications/patient preferences are not an issue? **-** *Please indicate **one drug** of choice:*	
☐ Metformin	☐ Sulfonylurea
☐ Thiazolidinediones	☐ SGLT-2
☐ GLP-1	☐ Insulin
☐ DDP-4 (gliptins)	☐ Insulin only
☐ Other	
20. Basic criterion used to select the above mentioned drugs - *Please tick all applicable:*	
☐ Proven clinical effectiveness	☐ Assessment of patient's individual clinical circumstances
☐ Recommended daily dose	☐ Extent of HbA1c elevation
☐ Patient's tendency to complain about side-effects	☐ Patient's age

☐ Cost of the drug

Use of evidence and literature when prescribing for adults with T2DM *- Please tick as appropriate:*

	Always	Often	Sometimes	Rarely	Never
21. When I prescribe, I mainly use the NICE 2015 guidance					
22. When I prescribe, I mainly use ressources obtained through courses financed by the practice/myself					
23. When I prescribe, I mainly follow the recommendations from my local CCG formulary					
24. When I prescribe, I mainly I follow proceedings/outcomes presented at relevant conferences					
25. When I prescribe, I follow the latest published evidence-based trial outcomes					
26. When I prescribe, I mainly follow recommendations by pharmaceutical sales representatives					
27. When I prescribe, I mainly follow recommendations from the secondary care diabetes team					

Insulin prescribing practice *- Please tick as appropriate:*

	Yes	No	Unsure
28. I *do not* ***initiate*** insulin prescribing			
29. I do not ***initiate*** insulin prescribing but some of my colleagues do			
30. After trying the ***drugs mentioned*** in ***Q17, Q18 and Q19*** I would refer the patient to an ***internal or external*** *diabetes* care team to have them initiated on insulin therapy			
31. In my practice we do not initiate insulin prescribing as it is not a part of the Primary Care Contract			

If you answered ***YES*** to ***Q28, Q29, and Q30***, please move on to **Q36**.

If you answered ***NO*** *to* ***Q28, Q29, and Q30***, please move on to **Q32**.

If you answered ***UNSURE*** *to any of the above questions,* please move on to **Q32**.

	Yes	No	Unsure
32. I would prescribe insulin as ***first-line treatment*** where HbA1c ***is more than 9%*** or if Type 1 diabetes is a possibility			
33. I would prescribe insulin as ***first-line treatment*** where ***HbA1c is more than 11%*** or if Type 1 diabetes is a possibility			
34. I would prescribe ***insulin as monotherapy*** after trying the drugs mentioned in ***Q17, Q18 and Q19***			
35. I would prescribe ***insulin as combination therapy*** after trying the drugs mentioned in ***Q17, Q18 and Q19***			

If you are in doubt about which medication to choose when treating an adult with T2DM in your daily practice who would you seek guidance from? *- Please tick as appropriate:*

	Always	Often	Sometimes	Rarely	Never
36. I would consult a ***general practitioner***					
37. I would consult a ***practice nurse***					
38. I would consult a ***diabetes specialist nurse***					
39. I would consult a ***pharmacist***					
40. I would ***contact*** the secondary care diabetes team and ask for advice					

41. I would refer patients to ***other healthcare professionals within the practice*** after trying the drugs mentioned in ***Q17, Q18 and Q19***					
42. I would refer patients to an ***in-house diabetes care team*** (with clinicians from secondary care) after trying the drugs mentioned in ***Q17, Q18 and Q19***					
43. I would refer patients to a ***secondary care diabetes team*** after trying the drugs mentioned in ***Q17, Q18 and Q19***					

For which reason of the following would you be seeking guidance from other healthcare professionals within the practice? - *Please tick as appropriate*

	Always	Often	Sometimes	Rarely	Never
44. Appropriate dose					
45. Patient presents with adverse drug reactions					
46. Patient presents with specific or difficult problems					
47. Polypharmacy concerns					
48. If I am uncertain of the therapeutically needs of the presenting patient					

For which reason of the following would you be seeking guidance from other healthcare professionals within the practice? - *Please tick as appropriate*

	Always	Often	Sometimes	Rarely	Never
49. Appropriate dose					
50. Patient presents with adverse drug reactions					
51. Patient presents with specific or difficult problems					
52. Polypharmacy concerns					
53. If I am uncertain of the therapeutically needs of the presenting patient					

Section E | Cost of T2DM medicines

	Yes	No	Unsure
54. In general, do you consider price of a medicine when prescribing a newly introduced drug?			
55. In your opinion, does the high price of a new drug imply better patient health outcomes?			
56. In general, do you compare the cost of new and old antidiabetic drugs?			
57. If two drugs from same drug class are appropriate have you ever chosen to prescribe one over the other due to cost?			
58. If two drugs in the same drug class are appropriate, have you ever chosen to prescribe one over the other due to recommendations from your local CCG?			
59. Does your practice receive a quarterly evaluation from the local CCG medicine management team?			
60. Does your local CCG medicine management team guide you on which ***generic brand*** to prescribe based on the cost of medicines?			

61. Does your local CCG medicine management team guide you on which ***drug class*** to prescribe based on the cost of medicines?			
62. Does your local CCG medicine management team guide you about the value of the prescribed medicines e.g. cost-effectiveness?			
63. The quarterly evaluation by the local CCG is an effective mechanism to contain (reduce) cost			
64. The quarterly evaluation by the local CCG encourages appropriate use of medicines			

End of questions

THANK YOU for completing this survey. Your responses will help inform evidence-based strategies to improve care
of patient suffering with T2DM.

Please could you kindly help us improve our survey by providing your

feedback on the next page

If you would like to be informed of the findings from our survey, please provide your details below:

Name:

Email address:

Please do not forget to send me back after cutting!

Appendix 19: Final questionnaire

Section A | About yourself

Sex			Age (years)					Qualification(s) and year of qualification(s)	Authorised to prescribe		Name of your local CCG
Female	Male	Prefer not to say	<30	31-40	41-50	51-60	>60		Yes	No	

Section B | About your practice

1. ***Which healthcare professionals at your practice are involved in the care of patients with T2DM?*** *- Please tick all that are applicable*

☐ General practitioner	☐ Practice nurse
☐ Diabetes specialist nurse	☐ Pharmacist

Please respond to the following statement as appropriate

	Yes	No	Unsure
2. Does your practice have an ***in-house diabetes care team*** treating patients with specific or difficult problems?			

Section C | Use of prescribing guidelines

Use of prescribing guidelines when prescribing for adults with T2DM *- Please tick as appropriate:*

	Yes	No	Unsure
3. Do you feel confident prescribing medicines for adults with T2DM based on current guidance provided by NICE?			
4. In your opinion, was the NICE 2015 treatment guideline [NG28] up-to-date with evidence ***at the time of publication in 2015?***			
5. In your opinion, is the NICE 2015 treatment guideline [NG28] up-to-date with ***current evidence*****?**			
6. Have you consulted the NICE guideline [NG28] ***for prescribing purposes*** in the past two weeks?			
7. Have you consulted the EASD/ADA guidelines ***for prescribing purposes*** in the past two weeks?			
8. Have you consulted the local CCG formulary ***for prescribing purposes*** in the past two weeks?			

How strongly do you agree/ disagree with following statements *- Please tick as appropriate:*

	Strongly agree	Agree	Undecided/ Neutral	Disagree	Strongly Disagree
9. In your opinion, are the drugs recommended by NICE in the NG28 guideline adequate to treat patients with T2DM?					
10. In your opinion, has NICE taken longer to update the current guideline on management of adults with T2DM compared to your local CCG?					
11. NICE is effective in managing the budget for medicines and achieves the widest possible range of medicines from the available funds					

12. There are adequate opportunities for primary care healthcare professionals to make their concerns known to NICE					
13. There is an adequate number of primary care representatives on the NICE committees					

Section D | Clinical management of adults with T2DM

Diet and exercise *- Please tick as appropriate:*

	Always	Often	Sometimes	Rarely	Never
14. When a patient is first diagnosed with T2DM do you offer diet and exercise as an intervention ***before*** initiating pharmacological treatment?					
15. When a patient is first diagnosed with T2DM do you offer diet and exercise ***along with*** pharmacological treatment?					

16. What is your preferred drug of choice at ***treatment initiation***, in most instances, if comorbidities/ contraindications/patient preferences are not an issue? *- Please indicate* ***one drug*** *of choice:*	
☐ Metformin	☐ Sulfonylurea
☐ Thiazolidinediones	☐ SGLT-2
☐ GLP-1	☐ Insulin
☐ DDP-4 (gliptins)	☐ Insulin only
☐ Other	

17. What is your preferred drug of choice at ***first treatment intensification***, in most instances, if comorbidities/ contraindications/patient preferences are not an issue? *- Please indicate* ***one drug*** *of choice:*	
☐ Metformin	☐ Sulfonylurea
☐ Thiazolidinediones	☐ SGLT-2
☐ GLP-1	☐ Insulin
☐ DDP-4 (gliptins)	☐ Insulin only
☐ Other	

18. What is your preferred drug of choice at ***second treatment intensification***, in most instances, if comorbidities/ contraindications/patient preferences are not an issue? *- Please indicate* ***one drug*** *of choice:*	
☐ Metformin	☐ Sulfonylurea
☐ Thiazolidinediones	☐ SGLT-2
☐ GLP-1	☐ Insulin
☐ DDP-4 (gliptins)	☐ Insulin only
☐ Other	

19. Your rationale of choosing a drug over the other is based on which criteria: - *Please tick all applicable:*	
☐ Proven clinical effectiveness	☐ Assessment of patient's individual clinical circumstances
☐ Familiarity with the dose	☐ Extent of HbA1c elevation
☐ Patient's tendency to complain about side-effects	☐ Patient's age
☐ Cost of the drug	

Use of evidence and literature when prescribing for adults with T2DM *- Please tick as appropriate:*

	Always	Often	Sometimes	Rarely	Never
20. When I prescribe, I mainly use resources obtained through courses					
21. When I prescribe, I follow the recommendations of the latest published clinical trials					
22. When I prescribe, I mainly follow recommendations by pharmaceutical sales representatives					
23. When I prescribe, I mainly follow recommendations from the secondary care diabetes team					

Insulin prescribing practice when prescribing for adults with T2DM *- Please tick as appropriate:*			
	Yes	No	Unsure
24. I initiate insulin prescribing			
25. I initiate insulin under the instruction of another prescriber i.e. supervised			
26. I initiate insulin prescribing but ***none*** of my colleagues do			
27. I ***do not*** initiate insulin prescribing but some of my colleagues do			
28. After trying the ***drugs mentioned in Q16, Q17 and Q18*** I would refer the patient to an ***internal*** *diabetes* care team to have them initiated on insulin therapy			
29. After trying the ***drugs mentioned in Q16, Q17 and Q18*** I would refer the patient to an ***external*** *diabetes* care team to have them initiated on insulin therapy			

If you answered ***YES*** to either ***Q24 or Q25***, please move on to **Q30**.

If you answered ***NO*** to ***Q24 or Q25***, please move on to **Q32**.

If you answered ***UNSURE*** *to either* ***Q24 or Q25***, please move on to **Q30**.

	Yes	No	Unsure
30. I would, in most instances***,*** prescribe ***insulin as monotherapy*** after trying the drugs mentioned in ***Q16, Q17 and Q18***			
31. I would, in most instances***,*** prescribe ***insulin as combination therapy*** after trying the drugs mentioned in ***Q16, Q17 and Q18***			

32. If you are in doubt about which medication to choose when treating an adult with T2DM in your daily practice who would you seek guidance from? *- Please tick as appropriate:*	
☐ A general practitioner	☐ A practice nurse
☐ A diabetes specialist nurse	☐ A pharmacist
☐ ***refer*** patients to an in-house diabetes care team	☐ ***contact*** secondary care diabetes team and ask for advice
☐ ***refer*** patients to a secondary care diabetes team	

For which reason of the following would you be seeking guidance? *- Please tick as appropriate*					
	Always	Often	Sometimes	Rarely	Never
33. Appropriate dose					
34. Patient presents with adverse drug reactions					
35. Patient presents with specific or difficult problems					
36. Polypharmacy concerns					
37. If I am uncertain of the therapeutically needs of the presenting patient					

Section E | Cost of T2DM medicines

	Yes	No	Unsure
38. In general, do you consider price of a medicine when prescribing for patients with T2DM?			
39. In general, do you compare the cost of new and old antidiabetic drugs?			
40. Does your local CCG medicine management team guide you on which ***generic brand*** to prescribe based on the cost of medicines?			
41. Does your local CCG medicine management team guide you on which ***drug class*** to prescribe based on the cost of medicines?			
42. Does your local CCG medicine management team guide you about the value of the prescribed medicines e.g. cost?			
43. Does your practice receive a quarterly evaluation from the local CCG medicine management team?			
44. In your opinion, is the quarterly evaluation by the local CCG an effective mechanism to contain (reduce) cost?			
45. In your opinion, does the quarterly evaluation by the local CCG encourage appropriate use of medicines?			

End of questions

THANK YOU for completing this survey. Your responses will help inform evidence-based strategies to improve care of patient suffering with T2DM.

If you would like to be informed of the findings from our survey, please provide your details below:

Name:

E-mail address:

Appendix 20: Number of responses from each CCG in Northern England

One response ***(n=24)***
Barnsley CCG
Blackpool CCG
Bolton CCG
Chorley & South Ribble CCG
East Lancashire CCG
Eastern Cheshire CCG
Fylde & Wyre CCG
Greater Preston CCG
Halton CCG
Hambleton, Richmondshire and Whitby CCG
Lancanshire CCG
North Cumbria CCG
North Durham CCG
North Tyneside CCG
Northumberland CCG
Salford CCG
Scarborough & Ryedale CCG
South Chesire CCG
Stockport CCG
Sunderland CCG
Vale Royal CCG
Warrington CCG
West Lancanshire CCG
Western Chesire CCG

Two responses ***(n=8)***
Bury CCG
Heywood, Middleton and Rochdale CCG
Leeds South and East CCG
Oldham CCG
Rotherham CCG
Trafford CCG
Wakefield CCG
Wirral CCG

Three responses ***(n=5)***
Bradford Districts CCG
East Riding of Yorkshire CCG
Liverpool CCG
Sheffield CCG
Vale of York CCG

Four responses ***(n=1)***
Bradford City CCG

Five responses ***(n=3)***
Darlington CCG
Doncaster CCG

South Tees CCG

Six responses ***(n=4)***

Central Manchester CCG

Durham Dales Easington & Sedgefield CCG

Greater Huddersfield CCG

Tameside & Glossop CCG

Seven responses ***(n=1)***

Hartlepool and Stockton-on-Tees CCG

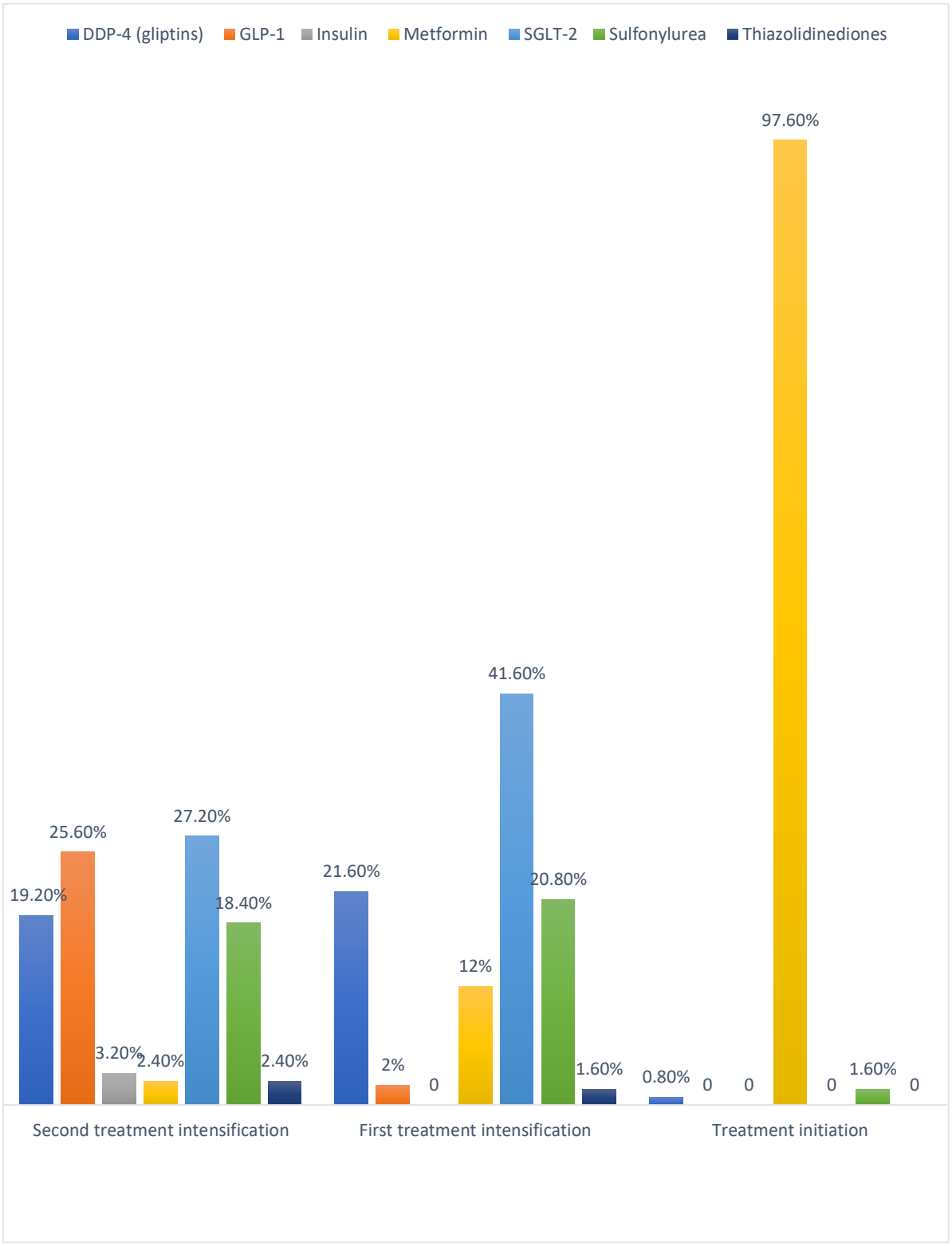
Eight responses ***(n=1)***

Newcastle & Gateshead CCG

Blank ***(n=10)***

Appendix 21: Respondents self-reported preferred choice of drug classes

Self-reported choices of drugs during treatment initiation, first treatment intensification and second treatment intensification if comorbidities/ contraindications/patient preferences are not an issue.



Appendix 22: Raw data ex-factory level prices in Euros.

	VIC18MG (£)	OZE0.25MG (£)	OZE0.50MG (£)	OZE1MG (£)
Austria	41.50	124.50	124.50	124.50
Belgium	39.87	85.10	85.10	85.10
Bulgaria	41.28	0.00	0.00	0.00
Switzerland	53.61	98.41	98.41	0.00
Cyprus	41.38	0.00	0.00	0.00
Czech Republic	45.08	125.06	125.06	0.00
Germany	44.27	73.63	73.63	73.63
Denmark	47.16	122.00	122.00	122.00
Estonia	39.82	95.84	95.84	95.84
Greece	43.11	103.63	103.63	103.63
Spain	41.76	93.28	93.28	93.28
Finland	39.09	88.92	88.92	88.92
France	38.63	68.32	68.32	68.32
Croatia	36.99	65.84	65.84	65.84
Hungary	39.50	94.04	94.04	94.04
Ireland	43.29	103.16	103.16	103.16
Italy	42.04	102.29	102.29	102.29
Lithuania	39.83	0.00	0.00	0.00
Luxembourg	44.30	0.00	0.00	0.00
Latvia	39.83	95.84	95.84	95.84
Malta	0.00	0.00	0.00	0.00
Netherlands	43.22	97.27	97.27	97.27
Norway	39.45	81.47	81.47	81.47
Poland	0.00	69.92	69.92	67.53
Portugal	42.04	0.00	0.00	0.00
Romania	40.20	0.00	0.00	0.00
Slovenia	44.25	80.44	80.44	80.44
Slowakia	0.00	76.88	76.88	0.00
Sweden	64.83	89.90	89.90	89.90
United Kingdom	38.54	76.22	76.22	76.22