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**Using the Health Policy Triangle Framework to
Describe Local, Regional and National Healthcare
Policy Changes within Ireland's Diverse Healthcare
Settings**

Thesis presented by

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Table of contents

List of tables	viii
List of figures	ix
List of abbreviations	x
Declaration	xiv
Publications resulting from this thesis	xv
Acknowledgements	xvi
Thesis abstract	1
Introduction	1
Methods	1
Results	2
Conclusion	4
1 Chapter 1 Introduction	5
1.1 Chapter description	5
1.2 Sláintecare	6
1.2.1 Sláintecare history	6
1.2.2 Sláintecare content and goals	11
1.3 Health policy	14
1.3.1 Health policy analysis	14
1.3.2 Health policy triangle	18
1.4 Evidence generation for use in health policy analysis	22
1.4.1 Research policy relationship	22
1.4.2 Health economic evaluations	23
1.4.3 Qualitative research	24
1.5 Health policy analysis and Sláintecare	25

1.5.1	Contemporary Irish health policy environment.....	25
1.5.2	Health policy frameworks and Sláintecare implementation	26
1.6	Hypothesis, aim, and objectives.....	27
1.6.1	Hypothesis.....	27
1.6.2	Thesis aim and objectives	28
1.6.3	Thesis outline	32
2	Chapter 2 Health policy triangle framework: narrative review of the recent literature	34
2.1	Chapter description	34
2.2	Publication.....	34
2.3	Abstract	35
2.3.1	Background	35
2.3.2	Objective	35
2.3.3	Methods	35
2.3.4	Results	35
2.3.5	Conclusion	36
2.4	Introduction.....	37
2.5	Methods	40
2.5.1	Literature search	40
2.5.2	Study selection	41
2.5.3	Study appraisal and data synthesis.....	42
2.6	Results	43
2.6.1	Search results	43
2.6.2	Study characteristics	45
2.6.3	Study findings.....	60
2.7	Discussion	64

2.7.1	Limitations.....	69
2.8	Conclusion	71
3	Chapter 3 Biosimilar infliximab introduction into the gastroenterology care pathway in a large acute teaching hospital: a review of policy change at local level.....	72
3.1	Chapter description	72
3.2	Publication.....	73
3.3	Abstract	74
3.3.1	Background	74
3.3.2	Objective	74
3.3.3	Methods	74
3.3.4	Results	75
3.3.5	Conclusion	75
3.4	Introduction.....	76
3.5	Methods	77
3.5.1	Content and Process	78
3.6	Results and discussion.....	86
3.6.1	Context	86
3.7	Conclusion	94
4	Chapter 4 Cost-effectiveness analysis of a physician-implemented medication screening tool in older hospitalised patients: evidence against policy change at local level.....	96
4.1	Chapter description	96
4.2	Publication.....	97
4.3	Abstract	98
4.3.1	Background	98
4.3.2	Objective	98

4.3.3	Methods	98
4.3.4	Results	99
4.3.5	Conclusion	99
4.4	Introduction.....	100
4.5	Methods	103
4.5.1	The prevention of ADRs in older hospitalised patients RCT	103
4.5.2	Economic evaluation	105
4.5.3	Guidelines and ethical considerations	111
4.6	Results	112
4.7	Discussion	117
4.7.1	Limitations.....	122
4.7.2	From evidence to policy.....	124
4.8	Conclusion	127
5	Chapter 5 Cost minimisation analysis of intravenous and subcutaneous trastuzumab treatment in patients with HER2-positive breast cancer: evidence for policy change at regional level.....	129
5.1	Chapter description	129
5.2	Publication.....	130
5.3	Abstract	131
5.3.1	Background	131
5.3.2	Objective	131
5.3.3	Methods	131
5.3.4	Results	131
5.3.5	Conclusion	132
5.4	Introduction.....	133
5.5	Methods	135

5.5.1	Hospital 1 – Nurse-led clinic.....	135
5.5.2	Hospital 2 – Infusion clinic	136
5.5.3	Cost minimisation analysis.....	136
5.5.4	Guidelines and ethical considerations	141
5.6	Results	142
5.6.1	Direct costs.....	142
5.6.2	Indirect costs	148
5.6.3	Total costs	148
5.7	Discussion	149
5.7.1	Limitations.....	152
5.7.2	From evidence to policy	154
5.8	Conclusion	157
6	Chapter 6 Out of pocket or out of control: a qualitative analysis of healthcare professional stakeholder involvement in pharmaceutical policy change at national level.....	159
6.1	Chapter description	159
6.2	Publication.....	160
6.3	Abstract	161
6.3.1	Background	161
6.3.2	Objective	161
6.3.3	Methods	161
6.3.4	Results	161
6.3.5	Conclusion	162
6.4	Introduction.....	163
6.5	Methods	167
6.5.1	Study design, setting and sampling	167

6.5.2	Data collection	169
6.5.3	Analysis.....	171
6.5.4	Guidelines and ethical considerations	172
6.6	Results	173
6.6.1	The withered tax-collecting pharmacist	174
6.6.2	The co-payment system – impact and sustainability.....	176
6.6.3	Concerns and prescribing patterns of physicians	180
6.7	Discussion	181
6.7.1	Limitations.....	184
6.7.2	From evidence to policy.....	186
6.8	Conclusion	188
7	Chapter 7 Discussion	190
7.1	Chapter description	190
7.2	Summary of findings.....	191
7.3	From evidence to policy	198
7.4	Strengths and limitations	201
7.5	Future research	210
7.6	Conclusion	211
	References	214
8	Appendices	249
8.1	Appendix I – All publications	250
8.2	Appendix II – Postgraduate taught modules completed	254
8.3	Appendix III – Training courses and conferences attended	255
8.4	Appendix IV - Chapter 2 Publication	257
8.5	Appendix V - Chapter 2 Framework descriptions	269
8.6	Appendix VI - Chapter 2 Search strategy.....	271

8.7	Appendix VII - Chapter 3 Publication	274
8.8	Appendix VIII - Chapter 4 Publication	283
8.9	Appendix IX - Chapter 4 Supplementary cost description	295
8.10	Appendix X - Chapter 4 Supplementary incremental cost-effectiveness analysis.....	296
8.11	Appendix XI - Chapter 4 Supplementary scenario analysis	298
8.12	Appendix XII - Chapter 4 Cheers checklist	299
8.13	Appendix XIII - Chapter 5 Publication	302
8.14	Appendix XIV - Chapter 5 Cheers checklist.....	313
8.15	Appendix XV - Chapter 5 Ethical approval.....	316
8.16	Appendix XVI - Chapter 6 Publication.....	321
8.17	Appendix XVII - Chapter 6 Participant information letter	330
8.18	Appendix XVIII - Chapter 6 Participant consent form.....	332
8.19	Appendix XIX - Chapter 6 Topic guides	333
8.20	Appendix XX - Chapter 6 COREQ checklist.....	338
8.21	Appendix XXI - Chapter 6 Ethical approval	341
8.22	Appendix XXII - Chapter 7 Policy brief	349

List of tables

Table 2.1 Inclusion and exclusion criteria	41
Table 2.2 Characteristics of included studies (listed alphabetically according to first author).....	46
Table 3.1 Topics under investigation in the Irish biosimilar consultation paper.....	91
Table 4.1 Baseline characteristics and trial-related outcomes of study population in the RCT	104
Table 4.2 Costs associated with care of patients in intervention arm in 2012.....	108
Table 4.3 Incremental cost-effectiveness analysis using 2012 data.....	114
Table 4.4 Scenario analysis using 2012 data.....	117
Table 5.1 Costs of healthcare workers.....	139
Table 5.2 Costs of consumables in patients treated with trastuzumab IV or trastuzumab SC during a treatment cycle.....	142
Table 5.3 Cost description associated with trastuzumab subcutaneous preparation, compounding and administration.....	145
Table 5.4 Cost description associated with trastuzumab intravenous preparation, compounding and administration.....	146
Table 5.5 Total costs in patients treated with trastuzumab IV or trastuzumab SC .	148
Table 6.1 Distribution of practices by location and ownership status	169
Table 6.2 Issues discussed in interviews	171
Table 6.3 Characteristics of interviewees	174
Table 7.1 Components of HPT framework from Chapters (3 - 6)	204

List of figures

Figure 1.1 Walt and Gilson policy triangle framework	19
Figure 1.2 Thesis outline	33, 192
Figure 2.1 Flow chart of study selection process.....	44
Figure 3.1 Independent systematic evidence base behind the decision-making process to implement biosimilar infliximab CT-P13 in a large acute Irish teaching hospital for the treatment of IBD	86
Figure 3.2 HPT framework describing biosimilar infliximab CT-P13 policy formation and implementation.....	93
Figure 4.1 Cost-effectiveness acceptability curve (controlling for treatment arm, age, sex, number of medications at admission and consultant (cluster group))	116
Figure 4.2 Walt and Gilson policy triangle model describing STOPP/START criteria policy formation, growth and evaluation	127
Figure 5.1 Common tasks conducted in the preparation and treatment of trastuzumab SC and IV	138
Figure 5.2 Walt and Gilson policy triangle model describing trastuzumab formulation switching policy.....	157
Figure 6.1 Timeline review of recent GMS co-payment introductions and changes 2010-2018	166
Figure 6.2 Walt and Gilson policy triangle model depicting the related factors pertaining to the pharmaceutical policy.....	188

List of abbreviations

ABF - Activity Based Funding

ACE - Angiotensin Converting Enzyme

ACF - Advocacy Coalition Framework

ADR - Adverse Drug Reaction

AIDS - Acquired Immune Deficiency Syndrome

BIA - Budget Impact Analysis

BSG - British Society of Gastroenterology

CAHC - Contemporaneously Available Healthcare Costs

CD - Crohn's Disease

CDSS - Clinical Decision Support Software

CEA - Cost-Effectiveness Analysis

CEAC - Cost-Effectiveness Acceptability Curve

CHEERS - Consolidated Health Economic Evaluation Reporting Standards

CHMP - Committee for Medicinal Products for Human Use

CI - Confidence Interval

CMA - Cost Minimisation Analysis

CNS - Clinical Nurse Specialist

CONSORT - Consolidated Standards of Reporting Trials

COREQ - Consolidated Criteria for Reporting Qualitative Research

DoH - Department of Health

EC - European Commission

ECCO - European Crohn's and Colitis Organisation

ECHO - Echocardiogram

EMA - European Medicines Agency

EMCONET - Employment and Working Conditions Knowledge Network

EU - European Union

GMS - General Medical Services

GP - General Practitioner/Physician

HCP - Healthcare Professional

HER - Human Epidermal Growth Factor Receptor

HIC - High-Income Country

HIV - Human Immunodeficiency Virus

HPRA - Health Products Regulatory Authority

HPT - Health Policy Triangle (Framework)

HPV - Human Papillomavirus

HRH - Human Resources for Health

HRQoL - Health-Related Quality of Life

HSE - Health Service Executive

IBD - Inflammatory Bowel Disease

ICER - Incremental Cost-Effectiveness Ratio

ID - Identification

IPA - Isopropyl Alcohol

IPHA - Irish Pharmaceutical Healthcare Association

IPU - Irish Pharmacy Union

IQR - Interquartile Range

ISPOR - International Society for Pharmacoeconomics and Outcomes Research

IT - Information Technology

IV - Intravenous

LAF - Laminar Air Flow Unit

LIC - Low-Income Country

LMIC - Lower-Middle-Income Country

LOS - Length of Stay

LTI - Long Term Illness

MeSH - Medical Subject Headings

MMP - Medicine Management Programme

NCCP - National Cancer Control Programme

NCPE - National Centre for Pharmacoeconomics

NHS - National Health Service

NICE - National Institute for Health and Care Excellence

NMS - New Medicines Service

NS - Non-Significant

OECD - Organisation for Economic Co-operation and Development

PCRS - Primary Care Reimbursement Services

PIM - Potentially Inappropriate Medication

PIP - Potentially Inappropriate Prescribing

PPO - Potential Prescribing Omission

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PRN - *Pro re nata* (as required)

QALY - Quality-Adjusted Life Year

RCT - Randomised Controlled Trial

SC - Subcutaneous

SD - Standard Deviation

SDG - Sustainable Development Goal

SID - Single-Use Injection Device

SMCE - Small Molecule Chemical Entity

SPRM - Structured Pharmacist Review of Medication

STOPP/START - Screening Tool of Older Persons' Prescriptions/Screening Tool to Alert doctors to Right Treatment

UC - Ulcerative Colitis

UCC - University College Cork

UHC - Universal Health(care) Coverage

UHI - Universal Health Insurance

UMIC - Upper-Middle-Income Country

UN - United Nations

UK - United Kingdom

USA - United States of America

VAT - Value Added Tax

WHO - World Health Organisation

Declaration

“This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism.”

Signed:

Date:

Publications resulting from this thesis

Chapter 2: O'Brien GL *et al.*, Health Policy Triangle Framework: Narrative Review of the Recent Literature, Health Policy OPEN, 2020, 1(1), DOI:10.1016/j.hpopen.2020.100016

Chapter 3: O'Brien GL *et al.*, Biosimilar Infliximab Introduction into the Gastroenterology Care Pathway in a Large Acute Irish Teaching Hospital: A Story behind the Evidence, Generics and Biosimilars Initiative Journal (GaBI Journal), 2018, 7(1):14-21, DOI:10.5639/gabij.2018.0701.004

Chapter 4: O'Brien GL *et al.*, Cost-Effectiveness Analysis of a Physician-Implemented Medication Screening Tool in Older Hospitalised Patients in Ireland, Drugs & Aging, 2018, 35(8):751-762, DOI:10.1007/s40266-018-0564-0

Chapter 5: O'Brien GL *et al.*, Cost Minimisation Analysis of Intravenous or Subcutaneous Trastuzumab Treatment in Patients with HER2-Positive Breast Cancer in Ireland, Clinical Breast Cancer, 2019, 19(3):e440-e451, DOI:10.1016/j.clbc.2019.01.011

Chapter 6: O'Brien GL *et al.*, Out of Pocket or Out of Control: A Qualitative Analysis of Healthcare Professional Stakeholder Involvement in Pharmaceutical Policy Change in Ireland, Health Policy, 2020, 124(4):411-418, DOI:10.1016/j.healthpol.2020.02.011

See Appendix I for a list of additional publications, Appendix II for postgraduate taught modules completed and Appendix III for training courses and conferences attended.

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Thesis abstract

Introduction

Developed in the late 20th century, the conceptual descriptive framework for this thesis was inspired by Walt and Gilson's health policy triangle (HPT). The HPT model is a policy analysis framework universally used and applied in the literature to analyse various health-related issues, mainly at national or international level. Robust research is required to seek a greater understanding of the application and utilisation of the HPT framework to describe smaller-scale health policy decisions under investigation at local and regional level. Such local and regional decisions may then inform both national and international decisions. The author's directive was to retrospectively analyse local, regional and national health policy change within different Irish healthcare settings over the last decade with regard to (i) development processes, (ii) evidence generation, (iii) implementation, and (iv) outcomes using the HPT framework within the context of the current Irish Sláintecare reforms.

Methods

Using diverse local, regional and national Irish healthcare settings, this thesis examined the generalisable nature of the HPT framework when applied to variety of health-related policy decisions at different stages in their life cycle. Methodologies such as literature reviews, economic evaluations (cost-effectiveness analysis and cost minimisation analysis), and qualitative analysis (using the Framework Approach) helped provide evidence on the health-related policy decisions.

Results

The narrative literature review in Chapter 2 identified that the types of health policies analysed by the HPT framework were mainly positioned at national or international level in lower to upper-middle-income countries and were primarily focused upon public health topics. This research concluded that given its generalisable nature, future research that utilises the HPT framework in smaller scale health policy decisions investigated at local and regional levels, could also be beneficial.

A subsequent literature review in Chapter 3 applied Walt and Gilson's health policy triangle model, as a scaffolding framework, to help describe how emerging evidence was used by a large acute Irish teaching hospital to permit the introduction of biosimilar infliximab CT-P13, for the treatment of IBD, into routine care in a safe and timely manner. The review of this local policy decision found that there was a significant time lag of over three years between regulatory approval and clinical acceptance for biosimilar infliximab CT-P13 in this large local hospital's switching process. The actors concluded that with the existential concern and uncertainty still surrounding biosimilar medicines, a distinct and individualised approach for biosimilar medicine implementation is required.

The cost-effectiveness analysis in Chapter 4 demonstrated that on average, the intervention arm of a physician-led medication review programme was more costly but was also more effective. Compared with usual care, the intervention was associated with a non-statistically significant increase of €877 (95% CI -€1,807, €3,561) in mean healthcare cost, and a statistically significant decrease of -0.164 (95% CI -0.257, -0.070) in the mean number of adverse drug reaction events per

inpatient. The HPT framework was used to describe how this local level policy decision concerning the physician-led STOPP/START intervention was not implemented but that the generated economic evidence contributed to the evolving STOPP/START criteria policy formation, growth and future evaluation.

The cost minimisation analysis in Chapter 5 assessed which formulation of trastuzumab (injected via different administration routes) was more cost-effective and time saving in relation to active healthcare professional (HCP) time. Over a full treatment course of 17 cycles, average HCP time saved accumulated to 16.78 hours with an estimated direct cost saving of €1,609.99 in favour of the trastuzumab subcutaneous formulation. The HPT framework elaborated on various contributing components concerning this contemporary regional policy which ultimately led to the replacement of the trastuzumab intravenous formulation by the trastuzumab subcutaneous formulation in clinical practice.

The qualitative interview study in Chapter 6 revealed that both community pharmacists and general practitioners (GPs) accepted the theoretical concept of a co-payment attached to the Irish public health insurance scheme as it prevents moral hazard. GPs independently suggested that a co-payment system introduced in their field of practice may inhibit moral hazard by publicly insured patients in the utilisation of GP services. The HPT framework was used to depict the interrelated factors which underpin this national pharmaceutical policy where going forward, both GP and pharmacy unions have expressed interest to be more involved in the policy formation stages, not the post-implementation stages.

Conclusion

This research has illustrated how generalisable and adaptable the HPT framework is when applied to health-related policy decisions in various Irish healthcare settings. Given this advantage, it is proposed that the HPT framework should be used in Sláintecare reform policy. Using a common descriptive framework and standardising the approach to health policy analysis during this ten-year reform has the potential to increase the successful fruition of Sláintecare policy goals.

1 Chapter 1 Introduction

1.1 Chapter description

This chapter provided an overview of the literature which informed the research detailed within this thesis. The chapter began by discussing Sláintecare: Ireland's ten-year plan for health reform, first published in May 2017. Its political history and overarching aim and objectives were explored. Secondly, the topic of health policy analysis was discussed. Some of the more commonly applied health policy analysis frameworks that are frequently used in the field were identified and defined. Additional attention was given to one health policy analysis framework in particular: the health policy triangle model. Following this, evidence generation in terms of health economic evaluations and qualitative research studies and how evidence of this nature supports the health-related policy decisions under investigation in this thesis was discussed. Thereafter, how the health policy triangle model can be retrospectively applied as an overarching framework to a variety of health-related policy decisions at local, regional and national level, using various case studies from the Irish healthcare system was described. The case for why this model could be incorporated and used as a common descriptive health policy framework in the analysis of all upcoming Sláintecare-related health policy decisions was outlined. Finally, the hypothesis underpinning this research and an outline of the overall aim and objectives of this thesis was presented.

1.2 Sláintecare

1.2.1 Sláintecare history

The Irish health system is frequently described as *'two-tier'*, where the national health service is funded predominantly through general taxation (1). There is no universal entitlement to public health care in Ireland, with eligibility varying according to residency, age and socioeconomic status (2). All residents are entitled to receive care in public hospitals free of charge or at a reduced cost. However, individuals with an income below a defined threshold or with certain medical conditions receive access to health services on the General Medical Services (GMS) scheme. The GMS scheme is a tax-funded, means-tested, public health insurance scheme (3). It provides many health benefits including access to primary care and hospital services free of charge and medicines with limited co-payments (4). Currently, 1.6 million (32%) of the Irish population receive healthcare on this scheme (5). Patients who avail of health coverage on the GMS scheme are known as medical card holders. Some other population groups (10 % of the population) have access to a general practitioner (GP) visit card that covers GP charges but does not cover the costs of medicines or hospital fees (6). The remaining population (58 %), who neither hold a medical card nor a GP visit card, must cover the costs of accessing GP services themselves (2).

In Ireland, more than two in five people purchase voluntary (private) health insurance which plays a supplementary role (2). In comparison to publicly insured patients, subscribers to private health insurance plans avoid long waiting times for specialist appointments and elective surgery in hospitals, but experience high premium costs (4). People are encouraged to buy private health insurance through substantial tax

subsidies, and since 2015, the Irish Government introduced lifetime community rating regulations which modified existing community rating regulations so that premiums individuals pay would increase with the age at which market entry took place. Subject to some exemptions, late entry loadings, set at 2% per year, apply to individuals 35 years of age and over who postpone market entry (7). Private health insurance does not fill all gaps in coverage e.g. It offers limited coverage of primary care and dental care; private health insurance subscriptions are heavily concentrated among richer people (4).

Overall, health spending per capita in Ireland is higher than other Organisation for Economic Co-operation and Development (OECD) countries notwithstanding that Ireland remains the only western European Union (EU) health system without universal healthcare coverage (UHC) for primary care (2). In 2019 for example, Ireland spent \$5,276 per capita on health, compared to the OCED average of \$4,224 (8). It has been long argued that the two-tier Irish healthcare system does not achieve sufficient *'bang for the buck'* (9, 10). Aware of this concern in 2011, the Irish Government decided to commit to the provision of UHC for the first time in the State's history. At the time, the Fine Gael [A right-leaning Irish political party] and Labour [A left-leaning Irish political party] majority coalition Government (2011-2016) stated their intention to establish *'a universal, single-tier health service, which guarantees access to medical care based on need, not income'* in their programme for Government on March 6th, 2011. This would be paid for by the introduction of a compulsory Universal Health Insurance (UHI) (11). In April 2014, a white paper on the topic of UHI entitled *'The Path to Universal Healthcare: White Paper on Universal Health Insurance'* published by then Minister for Health Dr. James Reilly, outlined

how UHC might be achieved. Under the proposed plans for UHI in Ireland, which closely resembled the Dutch model of social health insurance (12), all citizens would be insured for a standard package of primary and hospital care services, including mental health services; insurance would be provided under a multi-payer insurer model with no distinction between *'public'* and *'private'* patients (13). While health insurance would be mandatory, a system of financial support would ensure affordability by paying or subsidising the cost of insurance premia for all those who qualify (14). General taxation would remain the core financing mechanism (12).

However, a review conducted by the Economic and Social Research Institute shortly after concluded that the UHI initiative would be too costly to implement and would increase health care expenditure in Ireland by between 3.5% and 10.7% per annum (15). Ultimately, succeeding Minister for Health Dr. Leo Varadkar effectively ended the Government's pursuit of UHI, stating that a decision on funding would be taken *'in the latter part of the next Government term and implemented in the term thereafter'* (16). When the Fine Gael-Labour Government coalition disbanded on February 3rd, 2016, no real progress had been made on this front. In fact, there was a shift in focus to UHC without any specifics as to how to achieve universalism in 2015 where the Irish health system was considered less universal in 2015 than in 2011 (17).

The election campaign that followed the launch of Fine Gael's 2016 election manifesto reinstated its commitment to UHC and referred to the party's attempts to implement UHI during its time in Government. However, the manifesto did not proclaim a commitment to UHI implementation and instead stated that research into *'various models'* should be conducted (18). While Fine Gael had previously failed to

introduce UHC while in Government, the concept now appeared to be back on the policy agenda. At the same time, other Irish major political parties like Labour and Sinn Féin [A left-leaning Irish political party] discussed the concept of UHC on their political manifestos; Fianna Fáil [A right-leaning Irish political party] did not.

Fine Gael returned to power in 2016, but in a less powerful minority coalition with independent *Teachtaí Dála* [Members of Parliament]. On May 11th, 2016, the Programme for Partnership Government was published, and the new Fine Gael-Independent coalition stated its commitment to UHC. While this promise aligned with the previous Government's health policy, a parliamentary committee was established to oversee UHC execution '*to develop a single long term vision plan for healthcare over a ten-year period*' (19). Significantly, it was remarked that the plan '*should have cross-party consensus on healthcare planning and a shared vision*' (19). The idea of the cross-party committee had emerged on May 10th, 2016 when opposition Deputy Róisín Shortall, Social Democrats [A left-leaning Irish political party] co-leader launched a cross-party motion for a '*ten-year plan to deliver single-tier health service*', supported by 89 (56.3%) opposition Members of Parliament (out of a total of 158) (20).

On May 24th, 2016, Minister for Health Simon Harris proposed a motion to establish the cross-party committee. The Committee's membership would be balanced based on seats in Government: four members from the Fine Gael-Independent coalition, three from Fianna Fáil, two from Sinn Féin and one each from five smaller parties and parliamentary groups. The motion was welcomed by opposition parties. From June 2016 to May 2017, the Committee regularly met while also holding public hearings

and requesting written submissions from stakeholders. On May 30th, 2017, its work culminated in the publication of a report entitled '*Sláintecare*' (21). Given that multi-party agreement was now in place, a commitment to and action plan on how to implement and fund UHC began to emerge. The health system would be fundamentally reoriented: from two-tier to single tier; from hospital towards primary and social care settings e.g. by increasing access to diagnostics in the community. Moreover, access would be expanded by the provision of universal primary and GP care and by the removal of inpatient and emergency care charges. It was proposed that a national health fund, primarily financed by general taxation, would be established to fund the plan (21). Projected costings would necessitate investment of €2.844 billion over ten years and approximately €3 billion in transitional funding (21). Implementation timelines were outlined, and a *Sláintecare* Programme Implementation Office was established to bring effect to the plan.

Since the publication of the seminal *Sláintecare* report in May 2017, the Programme Implementation Office has refined the implementation strategy (which contained 106 sub-actions) into the 2019 programmatic action plan (22). Although progress to date has been slow, with early milestones missed and altered (23), health reform is being observed. On June 27th, 2020, a new Government comprising of a Fianna Fáil-Fine Gael-Green Party coalition was announced by the newly elected Taoiseach [Irish Prime Minister], Micheál Martin (24). Given that *Sláintecare* implementation is still in its early stages, this newly formed Government will have a pivotal role to enforce the implementation and to deliver upon the vision set out within the 2017 *Sláintecare* blueprint (21).

1.2.2 Sláintecare content and goals

Sláintecare is a 187-page document which outlines a ten-year plan to reform the Irish health system (21). The Committee's work plan included a commitment, *'to establish what healthcare entitlements should be covered under an agreed definition of universal healthcare'* (25). The Committee decided to adopt the following definition of universal healthcare based upon the World Health Organisation's (WHO) concept of UHC *'A universal healthcare system will provide population, promotive, preventative, primary, curative, rehabilitative and palliative health and social care services to the entire population of Ireland, ensuring timely access to quality, effective, integrated services on the basis of clinical need'* (21). The Sláintecare report comprises five main sections:

- i. Population health profile
- ii. Entitlements and access to healthcare
- iii. Integrated Care
- iv. Funding
- v. Implementation

(i) Population health profile

This section begins by examining the current demographics and health status of the Irish population. It then explores the social determinants of health and the ways in which they affect health outcomes and impact the health service. It concludes by discussing the various interventions that can be made in response, both at public health and health service levels e.g. the *'Healthy Ireland'* strategy (26). The Committee also recommend that the role of Minister of State for Health Promotion

should be retained in future Governments. This section of the report is informed by international evidence, submissions made to the Committee through consultations processes and current Irish policy and research.

(ii) Entitlements and access to healthcare

This segment of the report outlines the complexity of entitlements and access to services as experienced by the Irish population. In line with its commitment to the provision of UHC, the Committee proposes the introduction of a Cárta Sláinte [health card] which all residents in Ireland will have within five years of the reform plan being initiated. The Cárta Sláinte will entitle all those ordinarily resident to access care based on need. This part of the report also describes a remarkable expansion of care to meet population health needs, as well as the removal of private care from public hospitals (27). Interestingly, the policy agenda in the UK is moving towards increasing the amount of private practice in public hospitals, albeit from a much lower base than that in Ireland or Australia (28).

(iii) Integrated care

This section outlines the case and initial directions for the delivery of integrated care throughout the Irish health system. It builds on this by presenting the international evidence in favour of integrated care. It is centred on reorienting the system towards primary and community care; delivering care at the lowest level of complexity and empowering people to play a pivotal role in managing their own health. It reviews the critical challenges involved in developing integrated care throughout the Irish health system. It evaluates the required leadership and governance, funding mechanisms, information communications technology, workforce planning, and

analysis required to deliver integrated care by utilising the WHO health system building blocks *'The Committee's vision requires a system that is integrated in terms of all stages of an individual's life, from cradle to the grave, and also in terms of a comprehensive continuum of care from health promotion and disease prevention to diagnosis, treatment, disease management, rehabilitation and palliative care'* (21). It also addresses the obstacles posed by the current capacity constraints across the health system, including long waiting lists and emergency department overcrowding.

(iv) Funding

This part of the report explores the current financing of the Irish health budget and sets it in context internationally. It also explores the costs of funding a package of health service entitlements. The Committee recommends the establishment of a single national health fund which would include a mixture of general taxation and specific earmarked funds. They state that there should be a guaranteed expansion of health funding by between €380 and €465 million per year, for expanded entitlements and capacity to delivery UHC. The funding section also details the necessity for a €3 billion transitional fund to make up for a historical under investment in health, and to fund both physical and programme infrastructure to deliver a quality, integrated care in a timely manner.

(v) Implementation

One of the strongest concerns of the Committee on the Future of Healthcare is to ensure that this is not just another report on the health sector which is not implemented. The implementation section of the report clearly sets out the steps that must be taken to ensure effective implementation. Drawing on international and

national lessons on successful policy processes, this component outlines the *'how'* it should be done, and awareness that the nature of the policy cycle means that the policies should be continually designed, refined and reviewed as they are delivered. It also emphasises the importance of a whole system and process response to the report, how each section is interdependent on other sections and should not be handpicked for implementation.

In summary, Sláintecare details a ten-year plan for health reform with the aim of establishing a universal, single-tier health service where patients are treated solely on the basis of health need; reorienting of the health system *'towards integrated primary and community care, consistent with the highest quality of patient safety in as short a time-frame as possible'* (23). Its main objective is to provide universal access to timely, quality integrated care for all citizens in Ireland. As mentioned, a newly elected Government which comprises of a Fianna Fáil-Fine Gael-Green Party coalition was formed in late June 2020 (24). In line with the Sláintecare Programme Implementation Office, it is envisaged that this Government will provide the required continued political leadership and investment to support the delivery of sustained and progressive reform across the Irish health system.

1.3 Health policy

1.3.1 Health policy analysis

The WHO defines health policy as *'the decisions, plans, and actions (and inactions) undertaken to achieve specific health care goals within a society or undertaken by a*

set of institutions and organisations, at national, state and local level, to advance the public's health' (29). Health policy informs decisions like which health technologies to develop and utilise, how to structure and fund health services, and which pharmaceuticals will be freely available (30). Appreciating the intrinsic relationship between health policy and health, and the impact that other policies have on health, is crucial as it can help to address some of the major health problems that exist (31). However, health policy decisions are not always the result of a rational process of discussion and evaluation of how a particular objective should be met. The context in which the decisions are made can often be highly political and concern the degree of public provision of healthcare and who pays for it (32). Health policy decisions can also be conditional on the value judgements implicit in society. As a result, health policies do not always achieve their aims and implementation targets (33, 34). Consequently, health policy analysis is regularly undertaken to understand past policy failures and successes and to plan for future policy implementation (31).

Just as there are various definitions of what policy is, there are many ideas about the analysis of health policy, and its focus (30, 31). However, what a lot of health policy analysis studies have in common, whether that be analysis *of* policy or analysis *for* policy (35), is the use of a policy framework. A myriad of policy frameworks and theories exist (31). The burgeoning literature of health policy analysis sees novel policy frameworks being developed quite frequently with the '*policy cube*' approach being the latest addition (36). Some of the more commonly applied frameworks include stages heuristic model (37), the advocacy coalition framework (ACF) (38), Kingdon's multiple streams theory (39), the punctuated equilibrium framework (40) and the institutional analysis and development framework (40).

The stages heuristic is the '*idealistic*' to the policy process (37). It divides the policy process into a series of five stages:

- i. agenda setting
- ii. policy formulation
- iii. policy adoption
- iv. policy implementation
- v. policy assessment

This model has been widely criticised given that its linear, systematic approach to solving policy problems is rarely found. Nonetheless, it is helpful to think of policymaking occurring in these different stages (30).

The ACF was designed as an alternative to the stages heuristic; it intentionally avoids a linear description of the policy process (38). It addresses highly challenging issues in which there are substantial goal conflicts, important technical disputes and multiple actors from several levels of Government (40). The ACF examines the interaction within a policy subsystem of a small number of advocacy coalitions composed of actors from different institutions sharing similar policy beliefs (40). The ACF describes three tiers of beliefs:

- i. deep core beliefs
- ii. policy core beliefs
- iii. secondary beliefs

Kingdon's multiple streams theory within the policy process focuses on the role of policy '*entrepreneurs*' inside and outside Government who take advantage of agenda

setting opportunities '*policy windows*' and move items onto the Government's formal agenda (30). The model postulates that policy choices are made when the three streams (problem stream, policy stream and politics stream) intersect at pivotal time points '*policy windows*' where opportunities can occur spontaneously (39). When a policy window opens, the policy entrepreneur must immediately seize the opportunity to initiate action.

Punctuated equilibrium model theorises that the policymaking process is characterised by periods of stability with minimal or incremental policy change, disrupted by bursts of rapid transformation (31). The concept was initially developed in paleontology to explain sudden bursts of change in the fossil record scattered among longer-term minor changes (41). Central to the theory are the concepts of the '*policy image*' and the '*policy venue*'. The model has been used to explain the tendency for policy inactivity and sudden change in health policy issues like drug abuse and pesticide control in the USA (42).

The institutional analysis and development framework provides a language, and way of thinking about the means in which different institutions foster collective action. It highlights key insights on institutional, technical, and participatory aspects of collective interventions, or the commons problem, and their resulting effects (43). At the framework's core is the '*action arena*'. The action arena is composed of an action situation and actors and is used as the unit of analysis and investigation (44). The action situation refers to a social space where the actors interact, solve the commons problem, and exchange goods and services; the actors are those who participate in the situation (40). A major advantage of the framework is bringing an institutional

perspective to policy analysis, which does not appear to be as present in other frameworks.

Interest in conducting a policy analysis will presumably be driven by the knowledge of a particular health issue, existing evidence, and a particular policy area for further exploration. The aforementioned frameworks, models and theories have firmly carved out a position for themselves in the health policy process literature. Their use extends beyond the health sector where health policy analysts are researching means to improve their applicability and generalisability (45). All except the stages heuristic can be used to provide a comprehensive and explicit explanatory analysis. However, before this step can be achieved, it is often necessary to procure the '*raw materials*' by conducting an initial descriptive analysis of the health policy in question. In this regard, the health policy triangle (HPT) framework claims dominance over the health policy analysis literature (30).

1.3.2 Health policy triangle

The HPT framework was designed in 1994 by Walt and Gilson for the analysis of health sector policies, although its relevance extends beyond this field (46). The triangle model is a simplified framework grounded in a political economy perspective, and can be used to assess the feasibility of policy change by considering how four components (context, actors, content and process) interact (30). The framework helps investigate the power and politics of policymaking for a particular health policy. It explores the interrelationships of the four components in each stage of policy process in a systematic manner. The model originated when Walt and Gilson noted

that health policy research focused largely on the content of policy, neglecting actors, context and processes (**Figure 1.1**) (46).

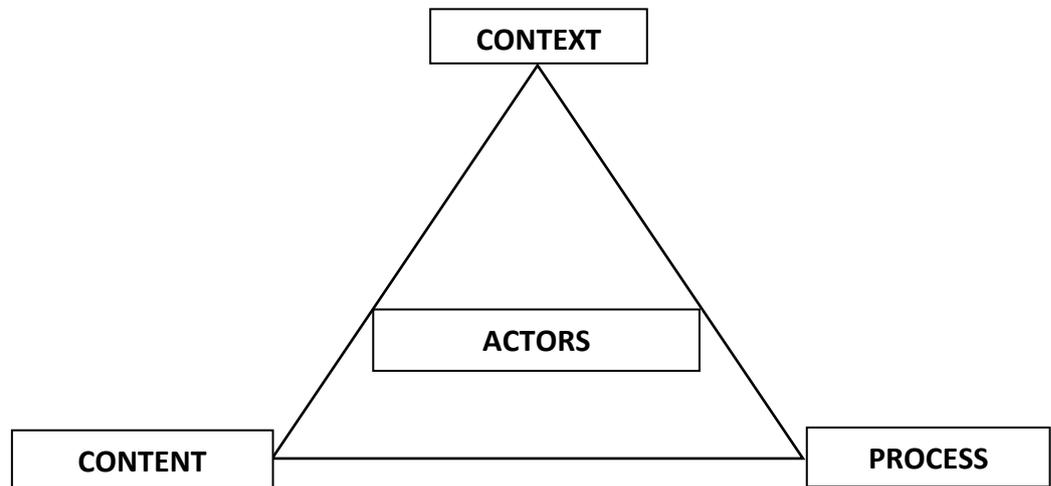


Figure 1.1 Walt and Gilson policy triangle framework

Policy context refers to systematic factors that have the potential to influence the policy process but are not part of the process. Such factors could be categorised as political, social, economic, cultural and other environmental conditions (30). Context can often be influenced by temporal and geospatial factors and thus is subject to change. To understand how health policies change, or do not, requires an ability to examine the context in which they are formed, and if possible, an assessment on how the contextual factors may influence policy outcomes.

Content forms the substance of a particular policy which details the subjects and topics covered (e.g. its specific objective and methods of implementation). It can be composed of policy objectives, operational policies, legislation, regulations, guidelines, and so much more. Traditionally, it was argued that many health policy analysts '*stopped*' at the content component of policy while neglecting the other

dimensions of process, actors and context which can make the difference between effective and ineffective policy choice and implementation (46). Content questions are concerned with the particular focus of a policy, its stated intentions and strategies to achieve its policy goal but are no longer the sole focus in health policy analysis (47).

The '*actors*' component of the HPT framework is placed in the centre of the model signifying its key role in relation to its interactions with context, content and process. Actors denote any influential participant in a policy process that has leverage on policymaking. Actors may be used to represent individuals, members of groups or organisations, or the State or Government. When classifying actors involvement in a particular health policy, it is important to recognise that individuals cannot be separated from the organisations within which they work where certain individuals may share different beliefs and values on the health policy in question (30). The extent of an actor's impact on the policy process is commensurate with their power level.

Power is defined as the ability to influence people and control resources to achieve a desired outcome by whatever means required (48). It is a key factor in the health policy process and an important element in determining the political feasibility of policy change from a political science perspective (49). Contextual factors may act as a source of power to instigate policy actors' action, inaction, and choice where actors can gain ascendancy within a specific environment to impact policy agenda setting and formulation processes (50). As noted by Mintzberg, to be an influencer, one requires some source of power – defined by control of a resource, a technical skill and body of knowledge, or stemming from a legal prerogative – or authority, coupled

with active involvement in ongoing processes in a politically skilful way (51). A stakeholder analysis can be conducted to elucidate the power levels that different actors obtain (52).

Process refers to the way in which policies are initiated, developed or formulated, negotiated, communicated, implemented and evaluated (30). While the policy process may seem or be presented in a linear fashion, analysts have criticised models like the stages heuristic for presuming a linearity to the public policy process that does not exist in reality, for postulating neat demarcations between stages that are blurred in practice, and for offering no propositions on causality (31, 40). Policymaking is an iterative process and is influenced by policy content, actors and context.

The HPT framework, which can be used retrospectively and prospectively, has influenced health policy research in many countries with diverse systems and has been used to analyse a large number of health issues (47). A review of literature has previously reported on the wide-ranging use of the HPT framework to understand many policy experiences in multiple lower-middle-income country (LMIC) settings (47). By investigating the application of the HPT framework to health policies in this context, such analysis can inform action to strengthen future global policy growth and implementation, and provide a basis for the development of policy analysis work. Given its broadly applicable nature, the policy triangle is a useful way to organise and think systematically about the various factors that might affect many different types of health-related policy decisions (30).

1.4 Evidence generation for use in health policy analysis

1.4.1 Research policy relationship

The relationship between research and policy is one that appears straightforward, yet when explored, is a highly complex one. There are different approaches to theorising the relationship between knowledge and policy (53); these include:

- i. knowledge shapes policy
- ii. politics shapes knowledge
- iii. co-production
- iv. autonomous spheres

The research generated from this thesis broadly aligns with the '*knowledge shapes policy*' theory or also known as the '*engineering*' model (30). This evidence-based policy approach focuses on how research can be used (instrumentally) to adjust, improve, or refine policy. On this account, policymakers draw on research and evidence to produce more effective policies. Notwithstanding criticism for being a rather simplistic, linear, rationalist model of the policy process, it permits policymakers to seek out the best evidence to adjust policy in a way that will improve policy outputs (53). The evidence generated in this thesis, which fed into the content component of the HPT framework for the particular health policy in question, comprises of both quantitative research (in the form of health economic evaluations) (54) and qualitative studies (using the Framework Approach) (55).

1.4.2 Health economic evaluations

Economic evaluation is defined as *'the systematic appraisal of costs and benefits of projects, normally undertaken to determine the relative economic efficiency of programs'* (54). Although its origins can be traced back to the 17th century (56), it has really only risen to prominence in the past 35 years and remains a relatively contemporary field of study. Improvements in the methodologies applied and increased confidence in outcomes associated with research in the field has helped health economics become more acceptable to all stakeholders especially health policy decision-makers (57). Two factors have mainly led to an increased use of economic evaluations by health policymakers. First, increasing pressures on health care budgets have led to a shift in focus from merely assessing clinical effectiveness, to one on assessing both clinical effectiveness and cost-effectiveness (54). Secondly, decision-making processes have emerged in several jurisdictions that enable the results of economic evaluations to be used as an integral part of funding, reimbursement, or coverage in health-related policy decisions (54). Full economic evaluations such as cost-effectiveness analyses are highly preferential sources of evidence for use by decision-makers as are economic analyses which adopt more than one perspective (58, 59), and budget impact analyses (BIAs) (60). Indeed, economic evaluations contribute to evidence-based decision-making in the health arena by helping policymakers and the community identify, measure, and compare activities with the necessary impact, scalability, and sustainability to optimise health (61).

1.4.3 Qualitative research

While heated discourse between qualitative and quantitative methodologists continues (62), it is now generally accepted that qualitative research methods can inform health-related policy decisions (63). One of the more commonly used analysis methods which originated in large-scale social policy research, but is becoming an increasingly popular approach in medical and health research, is the Framework Approach (64). The Framework Approach was developed during the 1980s at the National Centre for Social Research in the UK and is now widely used by qualitative researchers. The Framework Approach is a matrix-based method for analysing qualitative data. It facilitates data management such that all the stages involved in the analytic hierarchy can be conducted (64). This method is used by multidisciplinary health research teams which can be composed of nurses, doctors, pharmacists, sociologists, psychologists, epidemiologists, health economists, management scientists and others (55). Furthermore, as well as clinical representation, applied health research increasingly has patient and public involvement (65) where this analysis method is also accessible to them. Given its uncomplicated nature and origin in the policy arena, qualitative studies using the Framework Approach can shed explanatory and predictive light on important phenomena and contribute to the improvement of health services and development of health policy.

1.5 Health policy analysis and Sláintecare

1.5.1 Contemporary Irish health policy environment

Before the introduction of Sláintecare, the Irish health system had been particularly dominated by incremental change and a lack of reform/non-execution of reform implementation (17, 23). Despite the rhetoric of UHC circulating at the time, the Irish people endured years of austerity from the collapse of the Irish economy which began in 2007 (66). It led to poorer access to essential healthcare and little extension of population coverage (67). In 2015, the Irish health system was at a critical juncture, veering between a potential path to UHC and a system, overwhelmed by years of austerity, which maintained the status quo (17). Fortunately, the cross-party political consensus of the Committee on the Future of Healthcare ensured that Ireland has taken its first step in the direction of change and reform, veering away from the status quo (21).

Health policy processes are usually driven by the Department of Health (DoH), the Health Service Executive (HSE) or an expert group appointed by the Minister, the DoH or HSE. The policy process surrounding the initiation of Sláintecare is atypical due to the cross-party nature of the Committee and their consensual way of working (23). The process removes the governing party's politics from the policymaking process, but still situates health policymaking in the political domain (21). For whole system health reform on the scale of that proposed by the Committee, a clear and strategic implementation plan is recommended for health policies and strategies (68, 69). Thus, the Sláintecare Programme Implementation Office has refined the implementation strategy (which contained 106 sub-actions) into the 2019

programmatic action plan (22). However, what this ten-year health reform plan seems to be lacking is the use of conceptual health policy framework.

1.5.2 Health policy frameworks and Sláintecare implementation

Recent health policy analyses carried out on national health-related policy decisions such as palliative care, diabetes and chronic disease management in the Irish context used frameworks like the policy triangle model (33, 34, 70) and the Kingdon's multiple streams theory (34). However, there is little information available on local and regional health-related policy decisions in the Irish setting; HSE national divisions, hospitals and community health facilities around the country hold their own policies and procedures, many of which are not made publicly available (71). In 2008, Walt and colleagues commented on the paucity of theoretical frameworks in health policy analysis, *'the absence of explicit conceptual frameworks, little detail on research design and methodology, and a preponderance of single case studies on particular issues'* (31). They subsequently argued that *'To advance health policy analysis, researchers will need to use existing frameworks and theories of the public policy process more extensively'* (31). Thus, while health policy frameworks are being applied to some national policy decisions in Ireland, it is unknown if they're being used when analysing local and regional health-related policy decisions.

Burke *et al.* claim more research is needed to assess whether the political consensus achieved in Sláintecare's development will lead to the implementation of major health system reform to deliver UHC in Ireland (23). Throughout this thesis, it is professed that upcoming Sláintecare health policy decisions at local, regional and national level should apply a common descriptive health policy framework, in

particular, the Walt and Gilson policy triangle model (46). According to a suggestion made by Walt, theoretical models do not imply an approach to analysis but rather provide consistency and potential avenues for linking themes and concepts (31). The utilisation of a common descriptive framework means that all stakeholders can '*sing from the same hymn sheet*' in terms of health policy or funding decisions that must be made under Sláintecare reform. The work in this thesis retrospectively applies the policy triangle model to local, regional and national health-related policy decisions as an overarching descriptive framework given it is a policy analysis framework specifically for health, and has been used to analyse many health-related policy issues, all diverse in nature (47). Walt and Gilson have already demonstrated that retrospectively applying health policy frameworks to health-related issues can benefit future applications of frameworks when used prospectively (72). While the Sláintecare Programme Implementation Office has recently launched an implementation strategy in the 2019 programmatic action plan (22), its progress could potentially be ameliorated with the successful application of a health policy framework like the policy triangle model to its health-related policy decisions at local, regional and national level (31).

1.6 Hypothesis, aim, and objectives

1.6.1 Hypothesis

The Walt and Gilson policy triangle model is a policy analysis framework used ubiquitously in the literature to analyse a large number of health-related policy issues, almost all of which are positioned at national or international level (47).

Robust research is required to seek a greater understanding of the application and utilisation of the HPT framework to describe smaller-scale health policy decisions under investigation at local and regional level.

1.6.2 Thesis aim and objectives

The overarching aim of this thesis was to retrospectively analyse local, regional and national health policy change within different Irish healthcare settings over the last decade with regard to (i) development processes, (ii) evidence generation, (iii) implementation, and (iv) outcomes using the HPT framework.

Individual thesis objectives included:

- i. Conduct a review of the literature to explore and summarise the application of the HPT framework in health-related (public) policy decisions (Chapter 2).
- ii. Review and generate appropriate formal evidence, in the form of economic evaluations, for various health policy changes made at both local and regional level in the Irish secondary healthcare context (Chapters 3, 4 and 5).
- iii. Investigate an ongoing national pharmaceutical policy change, and key stakeholder involvement in that change, by means of qualitative analysis in the Irish primary care setting (Chapter 6).
- iv. Demonstrate the generalisable nature and novel application of the HPT framework to local, regional and national healthcare decisions in the Irish context with reference to its potential usefulness to decision-makers involved in Sláintecare reform and implementation (Chapters 1 and 7).

Chapter specific objectives included:

Chapter 2 - Health policy triangle framework: narrative review of the recent literature

- i. Review and summarise the literature concerning the application of the HPT framework in health-related (public) policy decisions from 2015 to 2020.
- ii. Identify which countries, classified by income, use the HPT framework as a means of policy analysis.
- iii. Reveal which genres of health policy fields commonly use the HPT framework.

Chapter 3 - Biosimilar infliximab introduction into the gastroenterology care pathway in a large acute teaching hospital: a review of policy change at local level

- i. Review how the first Irish hospital switched their inflammatory bowel disease patient cohort from originator infliximab to biosimilar infliximab CT-P13.
- ii. Explore evidence supporting the effective introduction and switching to biosimilar infliximab by means of a literature review.
- iii. Serve as a position paper by suggesting multiple evidence-based approaches to biosimilar medicine introduction in the absence of a national biosimilar policy in Ireland.

Chapter 4 - Cost-effectiveness analysis of a physician-implemented medication screening tool in older hospitalised patients: evidence against policy change at local level

- i. Perform an economic evaluation comparing the impact of the novel structured physician-led pharmaceutical regimen review compared with usual hospital care.
- ii. Use a multi-level mixed effect regression model to control for variables and construct a cost-effectiveness acceptability curve based on several hypothetical thresholds.
- iii. Use consolidated health economic evaluation reporting standards to ensure that the quality of the economic evaluation was of the highest international standard.

Chapter 5 - Cost minimisation analysis of intravenous or subcutaneous trastuzumab treatment in patients with HER2-positive breast cancer: evidence for policy change at regional level

- i. Compare trastuzumab treatment routes of administration in HER-2 positive breast cancer patients in the hospital setting and assess which route is more cost-effective and results in greater time savings for the healthcare professionals involved.
- ii. Perform sensitivity analyses to test the robustness of the results and various assumptions made in the economic evaluation.

- iii. Use consolidated health economic evaluation reporting standards to ensure that the quality of the economic evaluation was of the highest international standard.

Chapter 6 - Out of pocket or out of control: a qualitative analysis of healthcare professional stakeholder involvement in pharmaceutical policy change at national level

- i. Explore the involvement and perceptions of community pharmacists and general practitioners on a national pharmaceutical policy change.
- ii. Conduct semi-structured, face-to-face interviews and use the Framework Approach to analyse the data.
- iii. Use consolidated criteria for reporting qualitative research to ensure that the quality of the qualitative analysis was of the highest international standard.

Chapter 7 - Discussion

- i. Critically examine findings of previous chapters in terms of known information and consideration of new evidence generated by this research.
- ii. Examine the strengths and limitations of the major research findings.
- iii. State how research results were communicated to relevant policymakers.
- iv. Advocate for the use of the policy triangle model in assisting with health policy analysis under Sláintecare reform plans.

1.6.3 Thesis outline

Each of the individual thesis objectives outlined above are associated with a specific study chapter (Chapters 2 - 6), which are then followed by an overarching discussion chapter (Chapter 7). The author of this thesis was the primary investigator for all research presented within the thesis. The author was responsible for devising research strategies and implementing methodologies. The chapters described throughout provide the main evidence for this thesis. The conclusions and recommendations forthcoming from this thesis are based on the findings of Chapters (2 - 6) inclusive, where Chapters (2 - 6) are all published in academic peer reviewed journals. The author of this thesis is listed as the lead author on all external publications generated from work presented in this thesis.

This body of research illustrates how generalisable and adaptable the HPT framework is when applied to health-related policy decisions in various Irish healthcare settings. Given this advantage, it is proposed that the HPT framework should be used in Sláintecare reform policy. Using a common descriptive framework and standardising the approach to health policy analysis during this ten-year reform has the potential to increase the successful fruition of Sláintecare policy goals. **Figure 1.2** summarises how the individual studies undertaken as part of this doctoral research address the overarching aim and objectives of this thesis, and when combined, these chapters provide a comprehensive investigation into the analysis of local, regional and national health policy change within different healthcare settings in Ireland during recent times.

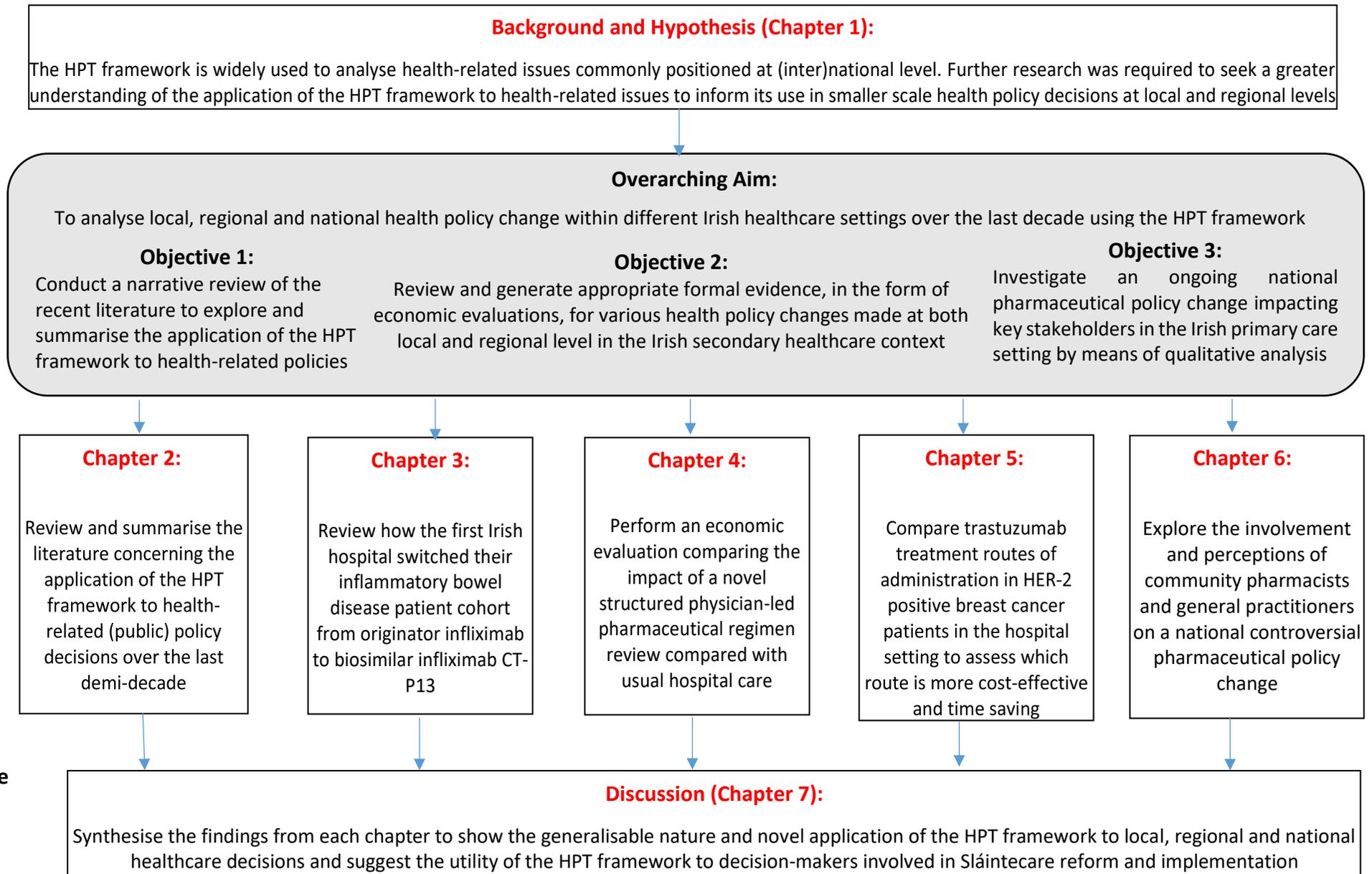


Figure 1.2
Thesis outline

2 Chapter 2 Health policy triangle framework: narrative review of the recent literature

2.1 Chapter description

This chapter collated the recent literature on health-related policy articles that use the policy triangle model as part of their policy analysis. The primary aim was to explore and summarise the application of the health policy triangle framework to health-related (public) policy decisions over the last demi-decade. This review helped inform the research questions and the health policy triangle framework applications seen in subsequent chapters. A literature search was conducted, and the retrieved literature was screened for eligibility. The study findings were summarised in a narrative format. The other authors of this chapter and publication reviewed the chapter and gave their input and advice during the study.

2.2 Publication

The work of this chapter has been published as O'Brien GL, Sinnott SJ, Walshe V, Mulcahy M, Byrne S, Health Policy Triangle Framework: Narrative Review of the Recent Literature, Health Policy OPEN, 2020, 1(1), DOI:10.1016/j.hpopen.2020.100016 (see Appendix IV for full text).

2.3 Abstract

2.3.1 Background

Developed in the late 20th century, the health policy triangle (HPT) is a policy analysis framework used and applied ubiquitously in the literature to analyse a large number of health-related issues.

2.3.2 Objective

To explore and summarise the application of the HPT framework to health-related (public) policy decisions in the recent literature.

2.3.3 Methods

This narrative review consisted of a systematic search and summary of included articles from January 2015 to January 2020. Six electronic databases were searched. Included studies were required to use the HPT framework as part of their policy analysis. Data were analysed using principles of thematic analysis.

2.3.4 Results

Of the 2,217 studies which were screened for inclusion, the final review comprised of 54 studies, mostly qualitative in nature. Five descriptive categorised themes emerged (i) health human resources, services and systems, (ii) communicable and non-communicable diseases, (iii) physical and mental health, (iv) antenatal and postnatal care and (v) miscellaneous. Most studies were conducted in lower to upper-middle-income countries.

2.3.5 Conclusion

This review identified that the types of health policies analysed were almost all positioned at national or international level and primarily concerned public health issues. Given its generalisable nature, future research that applies the HPT framework to smaller scale health policy decisions investigated at local and regional levels, could be beneficial.

2.4 Introduction

The WHO defines health policy as *'the decisions, plans, and actions (and inactions) undertaken to achieve specific health care goals within a society or undertaken by a set of institutions and organisations, at national, state and local level, to advance the public's health'* (29). Health policy informs decisions like which health technologies to develop and utilise, how to structure and fund health services, and which pharmaceuticals will be freely available (30). Appreciating the intrinsic relationship between health policy and health, and the impact that other policies have on health, is crucial as it can help to address some of the major health problems that exist. However, health policy decisions are not always the result of a rational process of discussion and evaluation of how a particular objective should be met. The context in which the decisions are made can often be highly political and concern the degree of public provision of healthcare and who pays for it (32). Health policy decisions can also be conditional on the value judgements implicit in society. As a result, health policies do not always achieve their aims and implementation targets (33, 34). Consequently, health policy analysis is regularly undertaken to understand past policy failures and successes and to plan for future policy implementation (31).

Just as there are various definitions of what policy is, there too are many ideas about the analysis of health policy, and its focus (30, 31). However, what a lot of health policy analysis studies have in common, whether that be analysis *of* policy or analysis *for* policy (35), is the use of a policy framework. A myriad of policy frameworks and theories exist (31). The burgeoning literature of health policy analysis sees novel policy frameworks being developed quite frequently with the *'policy cube'* approach

being the latest addition (36). A recent literature review investigated the application of some of the more commonly applied frameworks (44): the ACF (38), the stages heuristic model (37), the Kingdon's multiple streams theory (39), the punctuated equilibrium framework (40) and the institutional analysis and development framework (40). See **Appendix V** for brief descriptions of policy frameworks. While the review did mention the HPT framework as a means to help organise and think about the descriptive analysis of key variable types and to facilitate use of said information in one of the aforementioned political science theories/models, it did not investigate its application to public health policies.

The HPT framework was designed in 1994 by Walt and Gilson for the analysis of health sector policies, although its relevance extends beyond this sector (46). They noted that health policy research focused largely on the content of policy, neglecting actors, context and processes (**Figure 1.1**). Content includes policy objectives, operational policies, legislation, regulations, guidelines, etc. Actors refer to influential individuals, groups and organisations. Context refers to systemic factors: social, economic, political, cultural, and other environmental conditions. Process refers to the way in which policies are initiated, developed or formulated, negotiated, communicated, implemented and evaluated (30). The framework, which can be used retrospectively and prospectively, has influenced health policy research in many countries with diverse systems and has been used to analyse a large number of health issues (47).

In 2015, a historic new sustainable development agenda was unanimously adopted by 193 United Nations (UN) members (73). World leaders agreed to 17 sustainable

development goals (SDGs). These goals have the power to create a better world by 2030; they strive to end poverty, fight inequality and address the urgency of climate change. The SDGs call on all sectors of society to mobilise for action at a global, local and people level. Given that an estimated 40.5 million of the 56.9 million worldwide deaths were from non-communicable diseases in 2016 (74); approximately 810 women died every day from preventable causes related to pregnancy and childbirth in 2017 (73); an estimated 6.2 million children and adolescents under 15 years of age died mostly from preventable causes in 2018 (73); and approximately 38 million people globally were living with HIV in 2019 (73), SDG no. 3 aims to address these issues by ensuring healthy lives and promoting wellbeing for all (73). This goal has many sub-targets: to reduce maternal mortality; fight communicable diseases; end all preventable deaths under five years of age; promote mental health; achieve UHC; increase universal access to sexual and reproductive care, family planning and education; and many more. Fortunately, these health topics are regularly examined in the health policy literature and frequently analysed with policy frameworks like the policy triangle model (75-78).

Having established prominence in its field, the aim of this review is to explore and summarise the application of the HPT framework to health-related (public) policy decisions in the recent literature i.e. from January 2015 (corresponding with the year that the SDGs were launched) to January 2020. By investigating the application of the HPT framework to health policies during this time period, such analysis can inform action to strengthen future global policy growth and implementation in line with SDG no.3, and provide a basis for the development of policy analysis work. A review of past literature has previously reported on the wide-ranging use of the HPT framework

to understand many policy experiences in multiple LMIC settings only (47). This piece is the first literature review to include a compilation of health policy analysis studies using the HPT framework in both LMIC and high-income country (HIC) settings.

2.5 Methods

2.5.1 Literature search

The Medline, CINAHL Plus with Full Text, Web of Science (Core Collection), APA PsycInfo, PubMed and Embase databases were searched for primary, original literature in English published between 1st January 2015 and 31st January 2020. No Geofilter was applied to the searches. Given the subtle differences which exist between Medline and PubMed databases, it was deemed prudent to search both.

A search strategy was developed based on the use of index and free-text terms related to (i) Health Policy Triangle OR (ii) Policy Triangle Framework OR (iii) Policy Triangle Model. The lack of index terms to describe the HPT framework complicated the development of the search strategy. After much debate and perusal of the literature (44, 79), a qualified medical librarian reviewed and approved a search strategy prior to undertaking the literature searches. The search strategy was pre-tested prior to use to maximise sensitivity and specificity and to optimise the difference between both. See **Appendix VI** for the complete search strategy which attempted to include medical subject headings (MeSH) and Emtree terms and the use of Boolean operators.

Search results from multiple databases were transferred to a reference manager, End Note X9 (80). Due to the broad remit of the search strategy, a ‘*title review*’ stage was conducted to remove non-pertinent studies. Studies were removed in a cautious manner. An abstract review was then performed whereupon studies which clearly did not meet the inclusion criteria were excluded. The remaining studies underwent full-text review. To ensure consistency, one reviewer performed all stages of the review. Experts in academia were contacted to provide several suggestions for potentially pertinent studies. A ‘*snowballing*’ approach was used to identify additional literature through manual screening of the reference lists of the retrieved literature as well as the reference lists of such articles eligible for inclusion.

2.5.2 Study selection

The retrieved literature was screened for eligibility according to pre-specified inclusion and exclusion criteria (**Table 2.1**).

Table 2.1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
(i) Original primary research articles published in English between January 1 st , 2015 and January 31 st , 2020	(i) Articles not specifically related to health-related/public health policy issues
(ii) Articles interested in the application of the HPT framework to health-related/public health policy issues from countries of all income levels	(ii) Commentaries, conference abstracts, editorials, posters, (research/study) protocols, reports, and white papers
(iii) Articles addressing all four components of the HPT framework i.e. content of the policy; actors involved; process of policy development and implementation; context within which policy is developed	(iii) Book (chapters), (thesis) dissertations and grey literature

2.5.3 Study appraisal and data synthesis

The findings of each study included could not be pooled or combined as in systematic reviews or meta-analyses, and it was not deemed necessary to formally assess the study quality (81). Indeed, due to the nature of this review, not all of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were relevant, however, insofar as was practical; the PRISMA guidelines were followed (82). Instead, data from each study included in the review were extracted following guidance from similar studies (44, 83-85), the National Institute for Health and Care Excellence (NICE) (85) and from the Centre for Reviews and Dissemination's guidance for undertaking reviews in healthcare (86). Data were extracted and categorised according to country, country classification by income in 2020 (87), study design, data collection method, type and number of participants, type of analysis and health policy field i.e. non-communicable diseases, mental health, tobacco control, etc. The health policy field of the included studies were grouped according to similarity by applying the principles of thematic analysis (88, 89). Occasionally, ambiguity arose as to whether some of the included articles' content concerned health-related/public health policy issues, particularly in relation to the studies which investigated road traffic injury prevention (90) and domestic violence prevention and control (91). In such instances, a decision of eligibility for inclusion was made after consultation with a co-author.

2.6 Results

2.6.1 Search results

From the literature searches conducted in the six databases, a total of 2,217 citations were retrieved after the removal of duplicates. Based upon the title and abstract screening of the citations, 2,142 articles were excluded. Another 35 articles were excluded after reading the full texts. Considering the additional records identified through consultation with experts in the field and by handsearching bibliographies, a total of 54 studies were eligible for inclusion in the review. The process of study selection and reasons for exclusions are outlined in **Figure 2.1**. Corresponding authors of all conference abstracts (n=9) excluded were emailed to inquire whether a full-length manuscript of their work was published. The response rate was 100%. As of May 2020, no conference abstract had been published as a full-length manuscript.

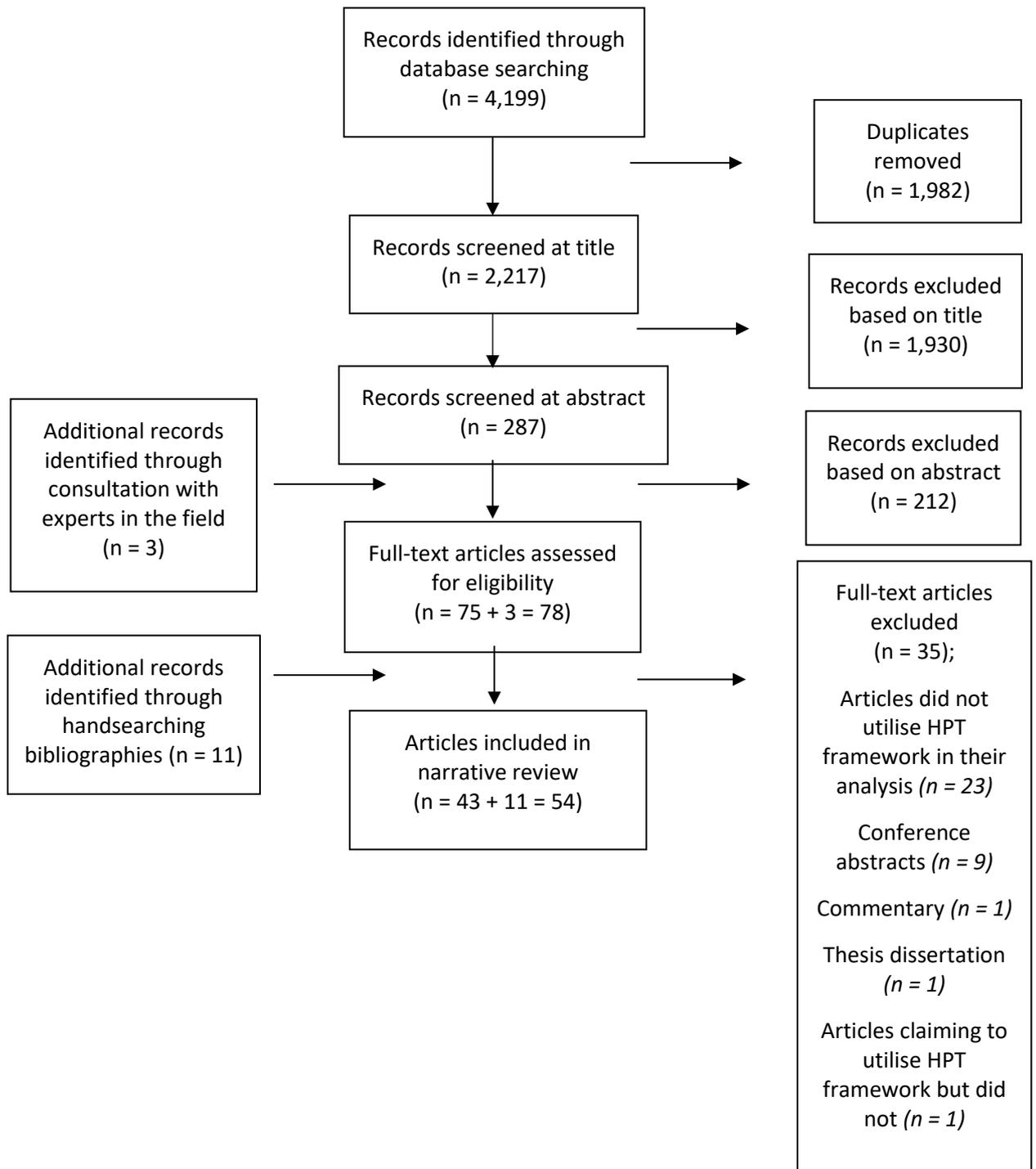


Figure 2.1 Flow chart of study selection process

2.6.2 Study characteristics

The characteristics of the 54 studies included in the review are summarised in **Table 2.2**. Forty-two of these studies describe themselves as having primarily used a qualitative study design. Data collection via various interview formats seemed to be the most common means of information retrieval. Eight of these studies would consider themselves to have a document analysis study design where one of the eight studies also included field work in its methodology. The remaining four studies can be described respectively as having a scoping review, mixed methods approach, literature review and theoretical analysis study design. According to country classification by income in 2020 (87), four of the included studies investigated low-income countries (LICs), 20 LMICs, 16 upper-middle-income countries (UMICs), and six HICs. Eight studies were classed as '*varied*' due to multiple countries of different classifications of income being simultaneously examined. All the included studies can be described as some variant of policy analysis. Certain articles highlighted whether the policy analysis was retrospective, prospective or comparative in nature; approximately 20% of the studies incorporated additional conceptual frameworks. Such additional details are outlined in the '*Type of analysis*' column in **Table 2.2**. Six studies conducted a supplementary stakeholder analysis/mapping (92).

Table 2.2 Characteristics of included studies (listed alphabetically according to first author)

Study, year	Country	Country classification by income in 2020 (87)	Study design	Data collection	Participants, (n)	Type of analysis	Health policy field
Abiona <i>et al.</i> (93), 2019	Nigeria	LMIC	Qualitative and scoping review	Key informant interviews, document and literature searches	Policy actors and bureaucrats, (n=44) Documents, (n=13)	Policy analysis	Alcohol-related policies
Abolhassani <i>et al.</i> (94), 2017	Iran	UMIC	Qualitative	Semi-structured interviews and document searches	Key informants, (n=31)	Policy analysis including stakeholder analysis	Medication safety policy to restrict look-alike medication names
Akgul <i>et al.</i> (95), 2017	Turkey	UMIC	Qualitative and literature review	Informal interviews, document and literature searches	Key actors, (n=?)	Retrospective policy analysis	Illegal drug policies
Alostad <i>et al.</i> (96), 2019	Bahrain and Kuwait	HIC and HIC	Qualitative	Semi-structured interviews, document searches and direct observation	Key officials, (n=23)	Policy analysis	Herbal medicine registration and regulation
Ansari <i>et al.</i> (97), 2018	Iran	UMIC	Qualitative	Semi-structured interviews	Stakeholders, (n=22)	Policy analysis	Palliative care policymaking

Study, year	Country	Country classification by income in 2020 (87)	Study design	Data collection	Participants, (n)	Type of analysis	Health policy field
Assan <i>et al.</i> (98), 2019	Ghana	LMIC	Qualitative	Semi-structured interviews	Participants, (n=67)	Policy analysis	Challenges to achieving UHC through community-based health planning and services delivery approach
Azami-Aghdash <i>et al.</i> (90), 2017	Iran	UMIC	Qualitative and literature review	Semi-structured interviews, document and literature searches	Stakeholders, (n=42)	Policy analysis	Road traffic injury prevention
Chen <i>et al.</i> (99), 2019	China	UMIC	Qualitative	Semi-structured interviews and document searches	Key actors, (n=15)	Policy analysis including stakeholder analysis	HPV vaccination programme
Doshmangir <i>et al.</i> (79), 2019	Iran	UMIC	Qualitative	Semi-structured interviews, document analysis and round-table discussion	Stakeholders, (n=23) Round-table discussion (constituting of senior policy makers, n=12)	Policy analysis (HPT incorporating the stages heuristic model)	UHC facilitation in primary healthcare

Study, year	Country	Country classification by income in 2020 (87)	Study design	Data collection	Participants, (n)	Type of analysis	Health policy field
Dussault <i>et al.</i> (100), 2016	Indonesia, Sudan and Tanzania	LMIC, LMIC and LIC	Field work and document analysis	Field research, document and literature searches	Direct contacts with relevant ministries and agencies, (n=5) Documents, (n=?)	Policy analysis	Implementation of the health workforce commitments announced at the third global forum on HRH
Etiaba <i>et al.</i> (101), 2015	Nigeria	LMIC	Qualitative and document review	In-depth interviews and document searches	Policy actors, (n=9)	Retrospective policy analysis	Oral health policy
Faraji <i>et al.</i> (102), 2015	Iran	UMIC	Document analysis	Document searches	Documents, (n=21)	Retrospective policy analysis	Diabetes prevention and control
Guo <i>et al.</i> (103), 2019	China	UMIC	Qualitative	Semi-structured interviews and document analysis	Key actors, (n=3)	Retrospective policy analysis	National adolescent mental health policy
Hafizan <i>et al.</i> (104), 2018	India, Thailand and Turkey	LMIC, UMIC and UMIC	Scoping review	Journal, article, report and book searches	Articles, (n=26)	Comparative policy analysis	Medical tourism policy

Study, year	Country	Country classification by income in 2020 (87)	Study design	Data collection	Participants, (n)	Type of analysis	Health policy field
Hansen <i>et al.</i> (105), 2017	Denmark	HIC	Literature review	Journal, article, newspaper and website searches	Articles, (n=11) Newspaper (n=14)	Prospective policy analysis (Kingdon model utilised in addition to HPT) ^a	Implementation of out-of-pocket payments to GPs
Islam <i>et al.</i> (106), 2018	Bangladesh	LMIC	Qualitative	In-depth interviews and document searches	Stakeholders, (n=42)	Policy analysis	Contracting-out urban primary health care
Joarder <i>et al.</i> (107), 2018	Bangladesh	LMIC	Qualitative and literature review	Key informant interviews, document and literature searches	Policy elites, (n=11)	Policy analysis including stakeholder analysis and mapping	Doctor retention in rural settings
Juma <i>et al.</i> (108), 2015	Kenya	LMIC	Qualitative and documents review	Semi-structured interviews and document searches	Stakeholders, (n=19) Documents, (n=14)	Retrospective policy analysis	Integrated community case management for childhood illness
Juma <i>et al.</i> (109, 110), 2018	Cameroon, Kenya, Malawi,	Varied	Qualitative and	Key informant interviews and document searches	Decision-makers, (n=202)	Policy analysis ^b	Multi-sectoral action in non-communicable disease prevention

Study, year	Country	Country classification by income in 2020 (87)	Study design	Data collection	Participants, (n)	Type of analysis	Health policy field
	Nigeria and South Africa		documents review		Documents, (n=276)		policy development and processes
Kaldor <i>et al.</i> (111), 2018	South Africa	UMIC	Qualitative	Semi-structured interviews	Stakeholders, (n=10)	Policy analysis	Regulation to limit salt intake and prevent non-communicable diseases
Khim <i>et al.</i> (112), 2017	Cambodia	LMIC	Qualitative and literature review	Key informant interviews, document and literature searches	Participants, (n=29) Documents, (n=?)	Policy analysis	Contracting of health services policy
Le <i>et al.</i> (91), 2019	Vietnam	LMIC	Qualitative and documents review	Key informant interviews and document searches	Policy actors, (n=36) Focus groups, (n=4) Documents, (n=63)	Policy analysis	Domestic violence prevention and control
Ma <i>et al.</i> (113), 2015	China	UMIC	Qualitative and literature review	In-depth interviews, document and literature searches	Key actors, (n=30)	Policy analysis	Task shifting of HIV/AIDS case management to

Study, year	Country	Country classification by income in 2020 (87)	Study design	Data collection	Participants, (n)	Type of analysis	Health policy field
					Focus groups, (n=15) Documents, (n=95)		community health service centres
Mambulu-Chikankheni <i>et al.</i> (114), 2018	South Africa	UMIC	Qualitative and document review	In-depth interviews and document searches	Stakeholders, (n=15) Patient records, (n=20)	Policy analysis	Role of community health workers in malnutrition management
Mapa-Tassou <i>et al.</i> (115), 2018	Cameroon	LMIC	Qualitative and document review	In-depth interviews and document searches	Stakeholders, (n=38) Documents, (n=19)	Policy analysis	Tobacco prevention and control policies
Mbachu <i>et al.</i> (116), 2016	Nigeria	LMIC	Qualitative and document review	In-depth interviews and document searches	Key informants, (n=10) Documents, (n=5)	Retrospective policy analysis	Integrated maternal newborn and child health
McNamara <i>et al.</i> (117), 2017	Trans-Pacific countries	Varied	Document analysis	Document search(es)	Documents, (n=1)	Prospective policy analysis (EMCONET framework used)	Trans-Pacific partnership agreement and associated

Study, year	Country	Country classification by income in 2020 (87)	Study design	Data collection	Participants, (n)	Type of analysis	Health policy field
						in addition to HPT) ^c	potentially serious health risks
Misfeldt <i>et al.</i> (118), 2017	Canada	HIC	Qualitative and document review	Key informant interviews and document searches	Stakeholders, (n=30) Documents, (n=119)	Comparative policy analysis	Team-based primary healthcare policies
Mohamed <i>et al.</i> (119), 2018	Kenya	LMIC	Qualitative and document review	Key informant interviews and document searches	Participants, (n=39) Documents, (n=24)	Policy analysis	Formulation and implementation of tobacco control policies
Mohseni <i>et al.</i> (120), 2019	Iran	UMIC	Qualitative and documents review	Semi-structured interviews and document searches	Informants and policymakers, (n=25)	Policy analysis (Kingdon model utilised in addition to HPT)	Prevention of malnutrition among children under five years of age
Mokitimi <i>et al.</i> (121), 2018	South Africa	UMIC	Document analysis	Document searches	Documents, (n=10)	Policy analysis	Child and adolescent mental health policy

Study, year	Country	Country classification by income in 2020 (87)	Study design	Data collection	Participants, (n)	Type of analysis	Health policy field
Moshiri <i>et al.</i> (122), 2015	Iran	UMIC	Qualitative and literature review	Semi-structured interviews document and literature searches	Key participants, (n=35)	Policy analysis (Kingdon model utilised in addition to HPT)	Formation of primary health care in rural Iran in the 1980s
Mukanu <i>et al.</i> (123), 2017	Zambia	LMIC	Qualitative and document review	Key informant interviews and document searches	Stakeholders, (n=8) Documents, (n=6)	Policy analysis	Non-communicable diseases policy response
Munabi-Babigumira <i>et al.</i> (124), 2019	Uganda	LIC	Qualitative and document review	In-depth interviews and document searches	Key informants, (n=18)	Policy analysis	Skilled birth attendance policy implementation
Mureithi <i>et al.</i> (125), 2018	South Africa	UMIC	Qualitative and documents review	Key informant interviews and document searches	Participants, (n=56) Focus groups, (n=3)	Policy analysis (Liu's conceptual framework used in addition to HPT) ^d	Emergence of three GP contracting-in models
Mwagomba <i>et al.</i> (126), 2018	Malawi	LIC	Qualitative and document review	Semi-structured interviews and document searches	Key informants, (n=32)	Policy analysis	Multi-sectoral action in the development of alcohol policies

Study, year	Country	Country classification by income in 2020 (87)	Study design	Data collection	Participants, (n)	Type of analysis	Health policy field
					Documents, (n=12)		
Nogueira-Jr <i>et al.</i> (127), 2018	Brazil, Chile, Israel	UMIC, HIC, HIC	Qualitative and document analysis	Non-structured interviews, observations and document searches	National team members, (n=?)	Policy analysis ^e	Implementation of national programs for the prevention and control of healthcare associated infections
O'Connell <i>et al.</i> (70), 2018	Australia, Canada, Ireland, Scotland, Wales	All HIC countries	Document analysis	Document searches	Documents, (n=8)	Comparative Policy analysis	Frameworks to improve self-management support for chronic diseases
Odoch <i>et al.</i> (128), 2015	Uganda	LIC	Document analysis	Document searches	Documents, (n=153)	Policy analysis (other framework used in addition to HPT) ^f	Male circumcision for HIV prevention policy process
Ohannessian <i>et al.</i> (129), 2018	France	HIC	Document and literature review	Document and literature searches	Documents, (n=?) Articles, (n=4)	Retrospective policy analysis	Non-implementation of HPV vaccination coverage in the pay

Study, year	Country	Country classification by income in 2020 (87)	Study design	Data collection	Participants, (n)	Type of analysis	Health policy field
							for performance scheme
Oladepo <i>et al.</i> (130), 2018	Nigeria	LMIC	Qualitative and document review	Key informant interviews and document searches	Stakeholders, (n=44) Documents, (n=18)	Policy analysis (other framework used in addition to HPT) ^g	Development and application of multi-sectoral action of tobacco control policies
Reeve <i>et al.</i> (131), 2018	Philippines	LMIC	Qualitative and literature review	Semi-structured interviews document and literature searches	Key informants, (n=21)	Policy analysis (components of ACF and Kingdon model utilised in addition to HPT)	School food policy development and implementation
Roy <i>et al.</i> (132), 2019	India	LMIC	Qualitative and document review	In-depth interviews and document searches	Key stakeholders, (n=11) Documents, (n=6)	Policy analysis including stakeholder analysis	Adolescent mental health policy
Saito <i>et al.</i> (133), 2015	Laos	LMIC	Qualitative and documents review	Key informant interviews and document searches	Policy implementers, (n=20)	Policy analysis	National school health policy implementation

Study, year	Country	Country classification by income in 2020 (87)	Study design	Data collection	Participants, (n)	Type of analysis	Health policy field
Shiroya <i>et al.</i> (134), 2019	Kenya	LMIC	Qualitative and documents review	Key informant interviews and document searches	Policy stakeholders, (n=6) Documents, (n=32)	Policy analysis	Translation of the UN declaration to national policies for diabetes prevention and control
Srivastava <i>et al.</i> (135), 2018	India	LMIC	Document and literature review	Document and literature searches	Documents, (n=22)	Retrospective policy analysis	Person-centered care in maternal and newborn health, family planning and abortion policies
Tokar <i>et al.</i> (136), 2019	Ukraine	LMIC	Qualitative and document review	Semi-structured interviews and document searches	Key stakeholders, (n=19) Documents, (n=75)	Policy analysis (other framework used in addition to HPT) ^h	HIV testing policies among female sex workers
Van de Pas <i>et al.</i> (137), 2019	Guinea	LIC	Mixed-methods approach	Semi-structured interviews and quantitative data collection	Key actors, (n=57)	Prospective policy analysis	Health workforce development and retention post-Ebola outbreak

Study, year	Country	Country classification by income in 2020 (87)	Study design	Data collection	Participants, (n)	Type of analysis	Health policy field
Van de Pas <i>et al.</i> (138), 2017	57 countries and 27 other entities	Varied	Qualitative and literature review	Semi-structured interviews document and literature searches	Government representatives from different countries, (n=25)	Policy analysis	Implementation of the HRH commitments announced at the third global forum on HRH
Vos <i>et al.</i> (139), 2016	Netherlands	HIC	Qualitative and document analysis	Semi-structured interviews and document searches	Key stakeholders, (n=12) Documents, (n=64)	Policy analysis including stakeholder analysis	Improvement of perinatal mortality
Wisdom <i>et al.</i> (140), 2018	Cameroon, Kenya, Nigeria, Malawi, South Africa, and Togo	Varied	Qualitative and documents review	Key informant interviews and document searches	Participants, (n=202) Documents, (n=?)	Policy analysis ⁱ	Influence of the WHO framework convention on tobacco control on tobacco legislation and policies
Witter <i>et al.</i> (141), 2016	Cambodia, Sierra Leone, Uganda and Zimbabwe	LMIC, LIC, LIC and LMIC	Qualitative and documents review	Key informant interviews and document searches	Participants, (n=109) Documents, (n=270)	Comparative policy analysis including stakeholder mapping	Patterns and drivers of HRH policymaking in post-conflict and post-crisis health systems

Study, year	Country	Country classification by income in 2020 (87)	Study design	Data collection	Participants, (n)	Type of analysis	Health policy field
Zhu <i>et al.</i> (142), 2018	China	UMIC	Qualitative and literature review	Semi-structured interviews, document and literature searches	Senior policy makers, (n=2)	Policy analysis ^j	Progress of midwifery-related policies
Zupanets <i>et al.</i> (143), 2018	Ukraine	LMIC	Theoretical analysis	Document and literature searches	Documents, (n=?)	Policy analysis ^k	Development of theoretical approaches to pharmaceutical care improvement and health system integration

Abbreviations: ACF - Advocacy Coalition Framework; AIDS - Acquired Immune Deficiency Syndrome; EMCONET - Employment and Working Conditions Knowledge Network; GP - General Practitioner/Physician; HIC - High-Income Country; HIV - Human Immunodeficiency Virus; HPT – Health Policy Triangle (Framework); HPV – Human Papillomavirus; HRH - Human Resources for Health; LIC - Low-Income Country; LMIC - Lower-Middle-Income Country; UHC – Universal Health Coverage; UMIC - Upper-Middle-Income Country; UN – United Nations; WHO – World Health Organisation; ? – Not specifically mentioned in related text

(a) Hansen *et al.* (105), 2017 - Content and process factors omitted in HPT analysis but justified elsewhere in manuscript

(b) Juma *et al.* (109, 110), 2018 - Juma *et al.* have published two study papers on a related topic from the same project using the same retrieved data sources. Thus, given the similarity, one data entry was deemed sufficient to encompass these two related study papers

(c) McNamara *et al.* (117), 2017 - A framework by the EMCONET of the WHO’s Commission on the Social Determinants of Health that comprehensively outlines pathways to health via labour markets (144)

(d) Mureithi *et al.* (125), 2018 - A conceptual framework by Liu *et al.* (145) on the impact of ‘contracting-out’ on health system performance

(e) Nogueira-Jr *et al.* (127), 2018 – Actor factor omitted in HPT analysis but justified elsewhere in manuscript

Study, year	Country	Country classification by income in 2020 (87)	Study design	Data collection	Participants, (n)	Type of analysis	Health policy field
<p>(f) Odoch <i>et al.</i> (128), 2015 – Bespoke frameworks used that were conceived from Walt and Gilson’s concepts for analysing the interrelationships between actors, process, and contexts (46). Odoch <i>et al.</i> also cited Kingdon’s multiple streams theory model (39), Foucault’s concept of power (146) and the Glassman <i>et al.</i> (147) concept of position mapping of actors, in their bespoke frameworks</p> <p>(g) Oladepo <i>et al.</i> (130), 2018 - Interview guides were informed by the Walt and Gilson policy analysis framework (46) and the McQueen analytical framework for intersectoral action (148)</p> <p>(h) Tokar <i>et al.</i> (136), 2019 - A framework analysis initially developed by Goffman <i>et al.</i> (149) and adapted by Caldwell <i>et al.</i> (150) was used in order to examine how the HIV/AIDS programme was conceptualised</p> <p>(i) Wisdom <i>et al.</i> (140), 2018 – Wisdom <i>et al.</i> use the same key informant interviews data source that was utilised by Juma <i>et al.</i> (109, 110)</p> <p>(j) Zhu <i>et al.</i> (142), 2018 – Authors purport to use a policy triangle framework proposed by Hawkes <i>et al.</i> (151). Upon further inspection and email contact with Hawkes, the framework used was in fact the HPT model originally proposed by Walt and Gilson (46) thus this study was included in the review. It is assumed that the authors accidentally miscited the policy triangle framework in their study</p> <p>(k) Zupanets <i>et al.</i> (143), 2018 – It is unclear which genre of study design best describes this article. For the purposes of this review, its study design was dubbed as a ‘<i>theoretical analysis</i>’</p>							

2.6.3 Study findings

From the content analysis approach to the health policy fields of the included studies, five broad descriptive categorised themes were identified demonstrating how the HPT framework was applied to health-related (public) policy decisions in the recent literature: (i) health human resources, services and systems, (ii) communicable and non-communicable diseases, (iii) physical and mental health, (iv) antenatal and postnatal care and (v) miscellaneous. Unsurprisingly, many of the health policy fields explored in the included studies aimed to address sub-targets of SDG no. 3 (73).

2.6.3.1 Health human resources, services and systems

The implementation of the human resources for health (HRH) commitments announced at the third global forum on HRH (152), with particular attention given to health workforce commitments, were analysed by two separate studies for different countries (100, 138). Another study by Witter *et al.* focused on the patterns and drivers of HRH policymaking in post-conflict and post-crisis health systems: namely those of Cambodia, Sierra Leone Uganda and Zimbabwe, all low to lower-middle-income countries. Similarly, Van de Pas *et al.* conducted a policy analysis study which sought to inform capacity development that aimed to strengthen public health systems, and health workforce development and retention, in a post-Ebola LIC setting (137). Indeed, a policy analysis on health workforce retention was also carried out by Joarder *et al.* where retaining doctors in rural areas of Bangladesh was a challenge (107).

Two studies looked at potential issues and policies surrounding UHC facilitation in the primary healthcare setting (79, 98). The somewhat related concept of contracting

health services arose in three studies where it was explored in relation to contracting for public healthcare delivery in rural Cambodia (112), contracting-out urban primary healthcare in Bangladesh (106), and the emergence of three GP contracting-in models in South Africa (125).

At primary and community healthcare level, a variety of policy analysis studies scrutinised topics like the formation of primary healthcare in rural Iran in the 1980s (122), contextual factors and actors that influenced policies on team-based primary healthcare in Canada (118), the potential implementation of out-of-pocket payments to GPs in Denmark (105), and policy resistance surrounding integrated community case management for childhood illness in Kenya (108).

There were three policy analysis studies which focused on medicines and pharmaceutical safety within the health system. Abolhassani *et al.* reviewed medication safety policy that saw the establishment of the drug naming committee to restrict look-alike medication names (94). Alostad *et al.* investigated herbal medicine registration systems policy (96) while Zupanets *et al.* sought to formulate theoretical approaches to the improvement of pharmaceutical care and health system integration (143).

2.6.3.2 Communicable and non-communicable diseases

The policy response to non-communicable diseases by the Ministry of Health in Zambia was explored by Mukanu *et al.* (123), where similarly, Juma *et al.* investigated non-communicable disease prevention policy development and processes, and how multi-sectoral action is involved (109, 110). Kaldor *et al.* analysed policy which used regulation to limit salt intake and prevent non-communicable diseases (111).

O'Connell *et al.* compared frameworks from different countries that aimed to improve self-management support for chronic (non-communicable) diseases (70). Two studies focused on diabetes, one of the leading non-communicable diseases worldwide, where prevention and control policies for the disease state were reviewed (102, 134).

Communicable disease policy analysis studies concentrated on two main viruses; human immunodeficiency virus (HIV) and human papillomavirus (HPV). Analyses in relation to HPV looked at the feasibility of implementation and non-implementation of a HPV vaccination programme in upper-middle to high-income countries (99, 129). HIV-related studies varied from policies like task shifting of HIV/AIDS case management to community health service centres (113), and male circumcision for HIV prevention (128), to HIV testing policies among female sex workers (136). Nogueira-Jr *et al.* investigated the implementation of national programs for the prevention and control of healthcare associated infections in three upper-middle to high-income countries (127).

2.6.3.3 Physical and mental health

Alcohol consumption, illegal drug ingestion, nutritional habits and tobacco inhalation are all potential determinants of the quality of physical health status. Four studies investigated varying factors surrounding tobacco control policies (115, 119, 130, 140). Two studies examined alcohol-related policies (93, 126) and one study scrutinised illegal drug policies (95). Three studies explored nutrition: two focusing on malnutrition management and prevention in UMICs (114, 120) and one reviewing school food policy development and implementation in the Philippines (131).

Interestingly, all three mental health policy analysis studies included in this review focused on the topic of child, and more frequently, adolescent mental health policy (103, 121, 132).

2.6.3.4 Antenatal and postnatal care

Policy analysis studies regarding pregnancy and mother and child wellbeing featured strongly. Zhu *et al.* outlined the progress of midwifery-related policies in contemporary and modern China (142) while Munabi-Babigumira *et al.* analysed the strategies implemented and bottlenecks experienced as Uganda's skilled birth attendance policy was launched (124). Other studies looked at the various factors which promoted or impeded agenda setting and the formulation of policy regarding perinatal healthcare reform (139), person-centered care in maternal and newborn health, family planning and abortion policies (135), and the integrated maternal newborn and child health strategy (116).

2.6.3.5 Miscellaneous

There were some other policy analysis studies that can be treated as standalone articles within the context of this review: palliative care system design (97); national law on domestic violence prevention and control within the health system (91); oral health policy development (101); road traffic injury prevention (90); national school health policy implementation (133); and medical tourism policy (104). Interestingly, given that the impact of the Trans-Pacific partnership agreement on employment and working conditions is a major point of contention in broader public debates worldwide (153), one prospective policy analysis study examined the potential health

impacts of the Trans-Pacific partnership agreement (154) by investigating labour market pathways (117).

2.7 Discussion

From the findings of this review, the most common method of data collection was by means of some form of interview with participants involved in the relevant policy area. The same finding was found in a similar review (47). Talking to actors can provide rich information for policy analysis. These collection methods may be the only way to gather valid information on the political interests and resources of relevant actors and to gather historical and contextual information. Indeed, interviews are generally more useful in eliciting information of a more sensitive nature where the goal of the interview is to obtain useful and valid data on stakeholders' perceptions of a given policy issue (30). However, interview data can be ambiguous in the sense that what interviewees say and the manner in which they say it, may contrast what one actually thinks or does. Many of the studies included in this review overcome this potential limitation by triangulating the responses with additional responses from other informants, or with data collected via alternative channels, particularly documentary sources.

Many different types of policy fields were unearthed throughout the data extraction process. Quite a lot of the studies reviewed large-scale health policies at national level whether that policy be UHC implementation, infectious disease vaccination programmes, or malnutrition management. Some studies conducted policy analysis at international level investigating areas such as the health impact of the Trans-Pacific

partnership agreement, and the implementation of the HRH commitments announced at the third global forum on HRH that involved over fifty countries. Cross-country comparative policy analysis was also common and examined topics like medical tourism, factors of HRH policymaking in post-crisis health systems, and frameworks to improve self-management support for chronic diseases. Indeed, health policy fields explored within the descriptive categorised theme '*miscellaneous*' demonstrated how wide-ranging the applicability of the HPT framework is to a variety of health-related (public) policy decisions. None of the included published literature explored policy analysis of local or regional health-related policy decisions using the HPT framework. Given its generalisable nature, further and perhaps more novel uses of the descriptive policy triangle model could be trialed in a diverse range of health policy decisions made at local and regional level.

Of the policy analysis study countries reviewed, approximately 40% were classified as LMIC settings. In recent years, such work has been incorporated into analysis of LMIC public sector reform experiences (47) thus possibly explaining this relatively high percentage. In addition, a reader recently published by WHO to encourage and deepen health policy analysis work in LMIC settings, which considers how to use health policy analysis prospectively to support health policy change, could explain this high percentage (155). Interestingly, notwithstanding that work conducted within the field of policy analysis is fairly well-established in the United States and Europe (156, 157), only approximately 12% of the policy analysis studies yielded from this review were conducted in HIC settings. This finding is open to many interpretations with one crude deduction being that perhaps policy analysis is currently more common in LMIC settings than in HIC settings. Another possibility is

that commissioned policy analysis studies in HIC settings are seldom published in peer reviewed academic journals. Also, it may be the case that LMIC settings rely on external academics to carry out and publish their health policy analysis studies as a recently published evidence assessment reports that LMICs often have an incomplete and fragmented policy framework for research (158). Further research is required.

All the included studies in this review can be described as some variant of policy analysis where certain articles specifically stated whether the policy analysis was retrospective, prospective or comparative in nature. In fact, the vast majority of studies can be categorised as analyses *of* policy rather than *for* policy (35). Most of the studies still seek to assist future policymaking, but are largely descriptive in nature, limiting understanding of policy change processes. Similar findings are found in the literature (47).

The comparative policy analysis studies included often involved more than one country with exception of the analysis by Misfeldt *et al.* who explored the context and factors shaping team-based primary healthcare policies in three Canadian provinces (118). Although such comparative studies may introduce further challenges (such as working across multiple languages and cultures, and procuring additional funding), the comparisons between similar (and different) country contexts can help disentangle generalisable effects from country context-specific effects in policy adaptation, evolution and implementation (31).

Six studies conducted a supplementary stakeholder analysis/mapping. Stakeholder analysis can be used to help understand about relevant actors, their intentions, interrelations, agendas, interests, and the influence or resources they have brought

or could bring on decision-making processes during policy development (52). The use of stakeholder analysis in this review was complemented by other policy analysis approaches as is corroborated by the literature (92).

Interestingly, approximately 20% of the studies in this review applied an additional analytical/theoretical framework. McNamara *et al.* used a framework by the Employment and Working Conditions Knowledge Network (EMCONET) of the WHO's Commission on the Social Determinants of Health (117) which comprehensively outlines pathways to health via labour markets (144). Mureithi *et al.* applied a conceptual framework by Liu *et al.* on the impact of contracting-out on health system performance (125, 145). Odoch *et al.* decided to implement many bespoke frameworks (128) that were conceived from Walt and Gilson's concepts for analysing the interrelationships between actors, process, and context (46) as well as citing the Kingdon's multiple streams theory model (39), Foucault's concept of power (146) and the Glassman *et al.* concept of position mapping of actors (147). Oladepo *et al.* utilised the McQueen analytical framework for intersectoral action (130, 148) while Tokar *et al.* incorporated a framework analysis that was initially developed by Goffman *et al.* and subsequently adapted by Caldwell *et al.* in order to examine how the HIV/AIDS programme in question was conceptualised (136, 149, 150). Given that there is a paucity of theoretical and conceptual approaches to analysis of the processes of health policy in LMIC settings (31, 72), the need to use multiple bespoke frameworks in the aforementioned recent policy analyses may be a plausible finding. In addition, other research has shown that the Walt and Gilson triangle model '*needs to be operationalised and transformed*' in practice which may suggest that it is not fit

for purpose in its primitive state (159). This could explain why auxiliary frameworks are applied alongside the HPT model in these studies.

Other studies applied the Kingdon model in addition to the HPT framework (105, 120, 122) where Reeve *et al.* used components of the ACF, Kingdon model and HPT framework (131). The policy triangle model is often regarded as being descriptive in nature (40, 44) thus supplementation with additional frameworks such as the ACF and Kingdon model can enrich the analysis by making it more explanatory (44). Doshmangir *et al.* used a tailored version of the HPT framework incorporating the stages heuristic model to guide data analysis (79). Like the policy triangle model, the stages heuristic are often characterised as being descriptive in nature (44), thus the aforementioned study provided a highly descriptive policy analysis of UHC facilitation in the primary healthcare setting in Iran. Unfortunately, no single policy framework offers a fully comprehensive description or understanding of the policy process as each model answers somewhat different questions (72, 160). Existing policy frameworks have complementary strengths since policy dynamics are driven by a multiplicity of causal paths (161). Thus, multiple frameworks can be applied as ‘tools’ in order to assess and plan action. However, it is important to discern which frameworks may be better suited for particular scenarios and policy issues (160).

Some of the 23 articles (see **Figure 2.1**) that were excluded from this review for not utilising the policy triangle model used other bespoke and well-known health policy frameworks, with the Kingdon’s multiple streams theory being the most common (39). As previously mentioned, a ‘snowballing’ approach was used to identify additional literature through manual screening of the reference lists of the retrieved

literature as well as the reference lists of such articles eligible for inclusion. Eleven additional studies were identified from this strategy (**Figure 2.1**) meaning many more were excluded for not meeting the inclusion criteria (**Table 2.1**). Such studies were too many to document. However, two articles identified from this process appeared to be quite misleading and thus noteworthy. Onwujekwe *et al.* described a conceptual model that they used in their policy analysis which was almost identical to the HPT framework (162). However, as the authors did not characterise or reference their framework to the policy triangle model or to the work of Walt and Gilson, it was omitted from the review. Similarly, Doshmangir *et al.* portrayed their results in such a way that correlated to the four components of the HPT framework (163). While the authors did mention the policy triangle framework as a talking point in their discussion section, they failed to explicitly reference it in their methodology and results paragraphs. This led to the exclusion of their study from the review. It is not known why these studies did not appropriately reference the utilisation of the HPT framework when its application was apparent. It is possible that more policy analysis studies which exist in the recent literature could be presented in a similarly ambiguous manner.

2.7.1 Limitations

The included articles were mostly qualitative in nature albeit other study designs were also utilised. Limitations inherent to such study designs may present a bias in the quality of the included articles. Grey literature including reports may have provided important sources of information regarding the application of the HPT framework to health-related (public) policy decisions. However, given the difficulty

associated with designing internet search strategies, the heterogenous nature of grey literature documents and the additional time required, it was excluded from the review (164). It was decided to only include primary English-language published literature on this topic from January 2015 to January 2020. It is recommended that additional reviews of other language literature be conducted in association with a wider time frame. This review does not claim to be a fully comprehensive summary of all policy analysis studies which utilised the HPT framework between 2015 and 2020. Further consultation with additional experts, citation searching methods, and handsearching of key journals may produce more relevant articles for inclusion. However, given that the majority of studies analysed thematically in this review are qualitative in nature, it can be argued that it is not necessary to locate every available study for such purposes (89, 165). In addition, it is known that some of the doctoral theses and unpublished material in the field are already represented within the published literature included here. Sometimes, the components of the HPT framework i.e. actors, content, context, process are described as such in the literature without exclusively referring to the HPT framework itself. Thus, these studies would not have been detected using the search strategy chosen for this review (**Appendix VI**). Finally, when compared to other research designs (e.g. systematic reviews), narrative reviews of the literature are more susceptible to bias e.g. the included articles were not evaluated for their quality (166).

2.8 Conclusion

This narrative review of the recent literature sought, retrieved and summarised the application of the HPT framework to health-related (public) policy decisions. Based on the findings of the review, it appears that the use of this framework appears to be ubiquitous in the health policy literature where many researchers supplement with additional health policy frameworks to further enhance their analysis. Notwithstanding a previous debate which disputes that there is a dearth of theoretical and conceptual approaches to analysis of the processes of health policy in low and middle-income countries (31, 72), this review demonstrates that the shortage of health policy analysis studies now appears to come from high-income countries. The finding suggests the need for additional health policy analyses to be conducted in such settings, or if this is already happening, the demand to publish more. In relation to the types of health policies being scrutinised, almost all were positioned at national or international level and primarily concerned public health issues. However, given its universal presence in the literature, and its unique adaptability and generalisability to many varied health policy topics, future research applying the HPT framework to smaller scale health policy decisions being investigated at local and regional levels, could be beneficial.

3 Chapter 3 Biosimilar infliximab introduction into the gastroenterology care pathway in a large acute teaching hospital: a review of policy change at local level

3.1 Chapter description

In this chapter, a health-related policy decision in a large acute Irish teaching hospital was investigated. The policy decision concerned the initiation and switching of patients to biosimilar infliximab CT-P13 from the originator medicinal product. It was decided to conduct a literature review on the supporting evidence behind such a policy decision. The HPT framework was applied as a scaffolding framework to describe the various contributing components which ultimately led to the successful implementation of the biosimilar policy. This study applied the policy triangle model to a health-related policy decision made at a local level; this has not been observed in the literature. The other authors of this chapter and publication reviewed the chapter and gave their input and advice during the review. On October 18th, 2018, the following published paper was submitted to the HSE-Medicines Management Programme in response to their national '*best-value biological medicines*' consultation; parts of the published paper helped inform version 2.0 of the '*MMP roadmap for the prescribing of best-value biological medicines in the Irish healthcare setting*' document published from the consultation process.

3.2 Publication

The work of this chapter has been modified and published as O'Brien GL, Carroll D, Mulcahy M, Walshe V, Courtney G, Byrne S, Biosimilar Infliximab Introduction into the Gastroenterology Care Pathway in a Large Acute Irish Teaching Hospital: A Story behind the Evidence, Generics and Biosimilars Initiative Journal (GaBI Journal), 2018, 7(1):14-21, DOI:10.5639/gabij.2018.0701.004 (see Appendix VII for full text).

3.3 Abstract

3.3.1 Background

Biosimilar medicines are not considered exact replicas of originator biologic medicines. As a result, prescribers can be hesitant to introduce such medicines into the clinical setting until evidence surfaces confirming their safety and effectiveness. In Ireland, a national biosimilar medicines policy is currently in development but the decision to prescribe biosimilar medicines remains at the discretion of the physician.

3.3.2 Objective

To describe how emerging evidence was used by a large acute Irish teaching hospital to permit the introduction of biosimilar infliximab CT-P13, for the treatment of inflammatory bowel disease (IBD), into routine care in a safe and timely manner.

3.3.3 Methods

The Walt and Gilson health policy triangle was applied as a scaffolding framework to help describe how the supporting evidence was used to effectively introduce biosimilar infliximab in a large acute Irish teaching hospital. A literature review was conducted which consisted of published studies, reviews, reports, position statements, articles, clinical guidelines and recommendations from national bodies, regulatory authorities and professional organisations. All evidence was published in English.

3.3.4 Results

In September 2014, the accumulated evidence base provided physicians with reassurance to prescribe biosimilar infliximab CT-P13 for new patients suffering from IBD in this large acute Irish teaching hospital. In September 2016, as the evidence base grew, physicians began to safely and confidently switch patients from the originator infliximab product to the biosimilar medicinal product.

3.3.5 Conclusion

There was a significant time lag between regulatory approval and clinical acceptance given that the European Medicines Agency (EMA) had granted market authorisation for biosimilar infliximab CT-P13 three years prior to the initiation of this hospital's switching process. Although conservative in their execution, the actors conclude that with the existential concern and uncertainty still surrounding biosimilar medicines, a distinct and individualised approach for biosimilar medicine implementation is required. It is hoped that the Irish biosimilar medicines policy will improve upon biosimilar medicine clinical acceptance once published.

3.4 Introduction

In 2014, six of the top 10 blockbuster medicines were monoclonal antibodies (167). In recent times, small molecule chemical entity (SMCE) blockbuster drugs like Viagra[®] and Lipitor[®], have been superseded by blockbuster biologics such as Humira[®] and Enbrel[®], demonstrating the newly acquired prominence of biological medicines (168, 169). However, these large complex proteins (comprised of or derived from living cells or organisms) are more complicated than traditional SMCEs due to their unique manufacturing process (170). Unlike generic drugs of SMCEs, biosimilar medicinal products (biosimilars) which aim to replicate originator biologic products, have given rise to concerns related to their pharmaceutical quality, safety (especially immunogenicity) and efficacy (particularly in extrapolated indications) (171, 172). This can create confusion around the practice of interchangeability which is not as lucid for biosimilars as it is for generic drugs of SMCEs (173).

Substitution, switching and interchangeability are terms often used when discussing biosimilars. Pharmacists can substitute generic drugs of SMCEs in Ireland and the UK on the proviso these medicines are deemed interchangeable (173-175). The European Medicines Agency (EMA) defines substitution as *'the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the prescriber'* whilst interchangeability refers to *'the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect'* (176). However, pharmacist substitution of biosimilars is not currently permitted in most countries (170, 177), although pharmacists practising in Australia can substitute some biological medicines (178). In the majority

of cases, it appears that pharmacists are bound by legislative constraints at the point of dispensing (179). As a result, physicians are the key stakeholders to switch patients to and from different brands of the same or similar biologic medicines, where switching is defined as *'when the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent'* (176).

There is no longer a dearth of evidence when it comes to the science and interchangeability status of biosimilar medicines. However, knowing when it is most appropriate and timely to implement these medicines into routine clinical practice can be difficult. In a large acute Irish teaching hospital, biosimilar infliximab CT-P13 was introduced in place of originator brand infliximab (Remicade®), to treat inflammatory bowel disease (IBD). As well as Crohn's disease (CD) and ulcerative colitis (UC), Remicade® is licensed to treat a range of other autoimmune diseases such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and psoriasis (180). In the absence of a national Irish biosimilar medicines policy and with perceived uncertainty surrounding biosimilar medicines, the aim of this descriptive review is to illustrate how emerging evidence was used by a large acute Irish teaching hospital to permit the introduction of biosimilar infliximab CT-P13, for the treatment of IBD, into routine care in a safe and timely manner.

3.5 Methods

The scaffolding framework for this review follows Walt and Gilson's HPT model which indicates how different actors interact to influence formulation, planning, implementation, and evaluation of health policies. This framework also helps to

assess perceptions, processes, and complexities of established strategies (46). In this review, components of the policy triangle have been applied retrospectively to describe the implementation of biosimilar infliximab CT-P13 in one large Irish acute hospital. It provides for understanding the processes through which influence is played out and how the actors and contemporary contextual factors shape and formulate the new biosimilar medicine policy for this healthcare setting (46). Recent evidence consisting of published studies, reviews, reports, position statements, articles, clinical guidelines and recommendations from national bodies, regulatory authorities and professional organisations were gathered and used by actors.

3.5.1 Content and Process

In June 2013, biosimilar infliximab was licenced by the EMA (181). The agency's committee for medicinal products for human use (CHMP) recommended the granting of marketing authorisations for the first two monoclonal antibody biosimilars, Remsima[®] and Inflectra[®], both of which contain the same known active substance infliximab CT-P13. The decision to provide marketing authorisation for both these infliximab biosimilar medicines was based on the same documentation. Their application dossiers demonstrated parallel similarity to the biological medicine Remicade[®], which has been authorised in the EU since 1999 (181). Remsima[®] and Inflectra[®] are recommended for authorisation in the same indications as Remicade[®].

A few weeks after biosimilar infliximab CT-P13 was licensed, the European Crohn's and Colitis Organisation (ECCO) released a position statement. They articulated within that post-marketing pharmacovigilance and unequivocal identification of infliximab CT-P13 as a biosimilar was in place. However, their overall stance on the

issue was that the use of most biosimilars in patients with IBD should require testing in this particular patient population with comparison to the appropriate innovator product (Remicade®) before approval (182). The ECCO also considered the benefits of wider access with appropriate use of biological therapy in IBD and potential direct cost savings important, but its primary concern was that rigorous testing was necessary in patients with IBD to ensure that appropriate efficacy and safety standards were met. The organisation was of the opinion that final clinical decisions should always be made on an individual basis, taking into account both the circumstances of the individual patient and the prescribing physician. The ECCO defied the practice of extrapolation for biosimilar infliximab at this time. In addition to stance taken by the ECCO, several national physician societies initially questioned marketing authorisations of biosimilars, including the extrapolation to IBD. It became obvious that there was a lack of understanding of the biosimilar development concept at this time (183).

Contrary to the guidance from the ECCO, the influencing actors of a large acute Irish teaching hospital i.e the chief pharmacist and consultant gastroenterologist, decided to introduce biosimilar infliximab CT-P13 for use in new patients in September 2014. Both parties had been documenting the evidence trail since the licencing of the biosimilar medicine in June 2013 and believed there was enough accumulated evidence from various sources to support their decision (181, 184). This information was relayed to all prescribing physicians during an internal staff meeting where the chief pharmacist and consultant gastroenterologist explained the science behind their evidence-based decision. All physicians accepted this decision and agreed to prescribe biosimilar infliximab CT-P13 for new patients in this setting. Physicians

agreed to report any adverse drug reactions (ADRs) to the Health Products Regulatory Authority (HPRA) in Ireland and to the EMA. Hospital budget co-ordinators were pleased given that the biosimilar product was cheaper than the originator brand. With verbal reassurance to patients on the safety and efficacy at the point of prescribing, physicians faced no opposition from new patients.

Although this new prescribing practice could have been deemed hasty, the British Society of Gastroenterology (BSG) released a position statement with updated guidance two months later where they justified the introduction of biosimilar infliximab CT-P13 in the clinical setting. The BSG recommended that infliximab should be prescribed by brand name (185). This prescribing practice contradicts the trend for SMCE medicines where prescribing generically is encouraged (173). This statement also proposed the use of a prospective registry of all biological use in IBD patients to capture safety data and side effects. For patients already on therapy, it was recommended to avoid switching from the originator product to the biosimilar, or vice versa, at least until safety data was made available (185).

During the summer of 2015, the National Institute for Health and Care Excellence (NICE) remarked positively on the topic of biosimilar prescribing. Their report concluded that the EMA was content that the pharmacokinetics, efficacy, safety and immunogenicity profiles of biosimilars were similar to those of the originator product and concluded that the recommendations for infliximab could apply both to the originator product and its biosimilars (186). In addition, the HPRA released a guide to biosimilars for healthcare professionals (HCPs) and patients in December 2015. This guide discussed the concept of extrapolation in the context of biosimilars where a

clinical study is carried out in one of the approved indications of the biological medicine and the efficacy data are then extrapolated to all authorised indications (177). As stated in this guide, extrapolation is not unique to the authorisation of biosimilars; a similar approach may also be used to deal with post-authorisation changes for reference biological medicines.

In February 2016, both the NICE and the BSG updated their previous guidance on the subject. The NICE reinforced that all HCPs should ensure biological medicines, including biosimilar medicines, are prescribed by brand name so that products cannot be automatically substituted at the point of dispensing. The choice of whether a patient receives a biosimilar or originator biological medicine should rest with the clinician in consultation with the patient (170). The BSG however decided to go one-step further, releasing a position statement on infliximab brand switching. Their guidance stated that there was sufficient evidence to recommend that patients who were in stable clinical response or remission on Remicade® therapy can be switched on the same dose and dose interval to biosimilar infliximab CT-P13. This switch should be carried out after discussion with individual patients and an accompanying explanation for switching (which is usually on the grounds of benefit to the overall service by reduction in costs of the drug and its administration) (185). Despite the position statement from the BSG, this large acute Irish teaching hospital judged that it was premature to switch all its patients from Remicade® to biosimilar infliximab CT-P13 at this time.

Two months later, a review entitled *'Switching to biosimilar infliximab (CT-P13): Evidence of clinical safety, effectiveness and impact on public health'* published in

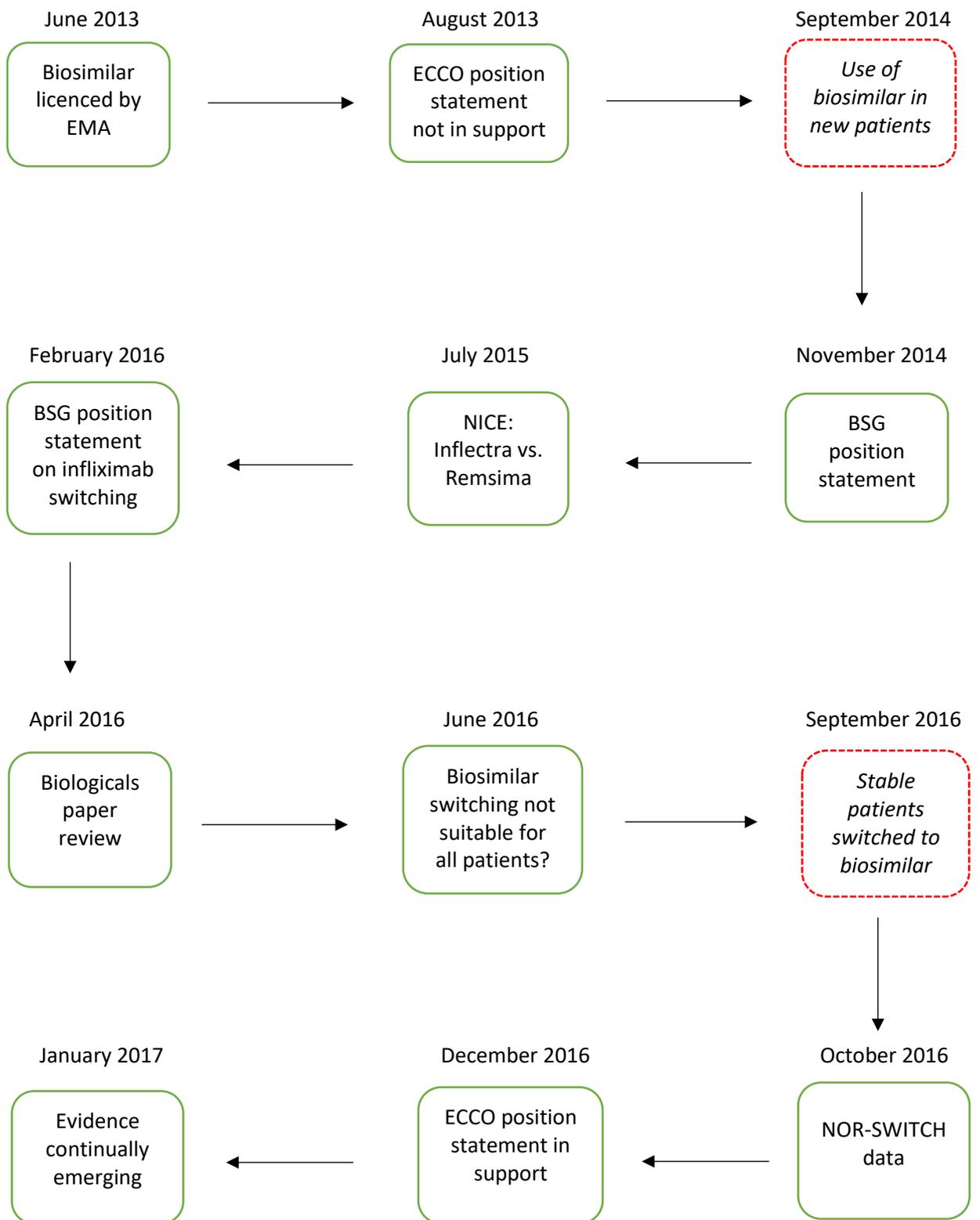
Biologicals journal concluded that whilst prudent switching practices should be employed, growing safety experience accumulated thus far with infliximab CT-P13 and other biosimilars was favourable and did not raise any specific concerns (187). Similar evidence that was in favour of switching had also started to surface (185, 188). In June 2016, ScienceDaily published a research article on their website entitled *'Biosimilar switching not suitable for all patients'* (189). At first, it appeared to the consultant gastroenterologist and chief pharmacist that this article, based on a study conducted in Spain (190), would counteract previous evidence in favour of switching. However, when examined closely, the results of the study showed that when antidrug antibodies develop in response to Remicade®, these antibodies also cross-react with biosimilar infliximab CT-P13 as both biologics share structural properties, including antigenic epitopes. These findings suggested that antibody-positive patients being treated with Remicade® should not be switched to biosimilar infliximab CT-P13 since these antibodies would also interact with the biosimilar and potentially lead to a loss of response. Despite its misleading title, the results of this research article actually emphasised the similarities between the originator and biosimilar brands of infliximab and strengthened the science behind the safety of switching. In fact, it should be reinforced that antidrug antibodies prevent a switch only if the exposure or clinical effect of the reference product is fading.

July 2016 saw the European Commission (EC) release guidance stating that biosimilars, despite small differences, were expected to be as safe and effective as the reference medicine (191). This publication followed previous documentation issued by the EC in 2014 explaining the concept of biosimilars to HCPs and the pharmaceutical industry (192). Therefore, based on all the continually emerging

evidence in favour of switching, the chief pharmacist and consultant gastroenterologist of the large acute Irish teaching hospital decided to switch all its patients from originator brand infliximab to biosimilar infliximab CT-P13 commencing in September 2016. This decision was relayed to all prescribing physicians during an internal staff meeting where the chief pharmacist and consultant gastroenterologist explained the science behind their evidence-based decision. All physicians accepted this and agreed to switch patients given the vast amount of evidence presented. Physicians agreed to report any ADRs to the HPRA and to the EMA. Hospital budget co-ordinators were once again pleased. Although physicians found it more challenging to reassure patients of the switch at first, they reported that after informing and addressing all patient concerns at the point of prescribing, no opposition to switching arose.

In October 2016, explorative subgroup analyses of patients with CD and UC in the NOR-SWITCH study showed similarity between patients treated with originator infliximab and biosimilar infliximab CT-P13 with regard to efficacy, safety and immunogenicity (193). Although this was one of the more large-scale controlled studies where biosimilar infliximab CT-P13 was tested in IBD patients, the small sample size of the IBD subgroup was too small to demonstrate any difference in ADR identification or minor differences in effect (193). However, it was still an advancement on previous evidence for switching which was justified on the concept of extrapolation. The ECCO released an updated statement in December 2016 that revised its previous guidelines. One of the prominent recommendations was that switching IBD patients from the originator brand to a biosimilar product was now deemed acceptable. It also stated that studies of switching can provide valuable

evidence for safety and efficacy and that scientific and clinical evidence is lacking regarding reverse switching, multiple switching, and cross-switching among biosimilars in IBD patients (194). In this rapidly moving field, the evidence is continuing to grow supporting the case that biosimilar infliximab CT-P13 is just as safe and effective as the originator biologic. **Figure 3.1** illustrates in diagrammatic form, the systematic trail of evidence behind the decision-making process to introduce and switch patients to biosimilar infliximab CT-P13 in this large acute Irish teaching hospital.



Key: BSG: British Society of Gastroenterology; ECCO: European Crohn's and Colitis Organisation; EMA: European Medicines Agency; IBD: inflammatory bowel disease; NICE: National Institute for Health and Care Excellence

Figure 3.1 Independent systematic evidence base behind the decision-making process to implement biosimilar infliximab CT-P13 in a large acute Irish teaching hospital for the treatment of IBD

3.6 Results and discussion

3.6.1 Context

The decision to treat new and switch existing patients to biosimilar infliximab CT-P13 in this large acute Irish teaching hospital was a multifactorial one underpinned by a robust and extensive evidence-based trail that ultimately convinced prescribing physicians. From September 2014, all new patients requiring infliximab therapy for the treatment of IBD were prescribed biosimilar infliximab CT-P13. In September 2016, all IBD patients receiving Remicade® were switched to biosimilar infliximab CT-P13. Switching from originator infliximab to biosimilar infliximab CT-P13 in IBD patients occurred in this hospital before any other Irish hospital and before the release of the NOR-SWITCH study data. Biosimilar infliximab CT-P13 was first licensed in June 2013 (181) but it was not until approximately three years later that prescribers in this large acute Irish teaching hospital decided to switch patients. It is evident that there was a significant time lag between regulatory approval and clinical acceptance. In fact, Ireland has the second lowest record of biosimilar use due to Irish HCPs being slow to accept biosimilars (195, 196). This is possibly owing to a lack of confidence, unwillingness or knowledge to prescribe biosimilars which is also seen in other European countries (197). Work which aims to enhance the understanding of biosimilar medicines amongst stakeholders and to encourage best practice of biosimilar use is currently being conducted by a collaborative organisation of various

interested parties (198, 199). However, it could be argued that Ireland has exceptionally low biosimilar uptake because biosimilar prescribing is not mandated unlike in other countries (200). In addition, the Irish biosimilar market does not appear very appealing to pharmaceutical companies. Despite the potentially huge cost savings to be made from switching, only 54 packets of the biosimilar product Benepali® were sold since its introduction to Ireland in August 2016 compared to almost 46,856 of the established originator brand Enbrel® (as of May 2017) (201). Furthermore, various funding systems of different countries can too have an impact where, for example in the UK, a major motivation for switching was reinvestment of some of the cost savings in improvements to patients' care (186).

The decision by this Irish teaching hospital to switch patients to biosimilar infliximab could have been regarded as over cautious, delayed and conservative given that the EMA had already licensed the biosimilar medicine three years earlier (181) and thus, one wonders why prescribers had not switched patients sooner. With regard to the current biosimilar medicine landscape, it is possible that prescribers may feel more comfortable issuing biosimilars if national authorities would actively enforce and implement individual EMA biosimilar-related decisions as they are published. The EMA has the best knowledge of biosimilars amongst regulators but cannot influence interchangeability that is within the mandate of individual national regulatory agencies (176). These authorities have different capacities to produce information on biosimilars and as a result, this predicament contributes to the differential rate of acceptance of biosimilars within EU member states. With continually emerging positive evidence, it is clear that a three-year time lag for the next biosimilar medicine, from market authorisation to the patient switching process, should not

occur. Flixabi[®], biosimilar infliximab SB2 (202), received market authorisation approximately three years after biosimilar infliximab CT-P13 (203). Given its late entry in the field relative to biosimilar infliximab CT-P13, it has been unsuccessful in penetrating the Irish market so far. Both the chief pharmacist and consultant gastroenterologist of this teaching hospital note that they would not be comfortable in switching patients from biosimilar infliximab CT-P13 to biosimilar infliximab SB2 without conducting a comprehensive review of the available evidence, (especially evidence from a switching study), even if the national regulator did declare all licensed biosimilars completely interchangeable (177). Interestingly however, this large acute Irish teaching hospital were content to switch patients to Tevagrastim[®], a biosimilar of filgrastim (204), from the originator brand without performing such a robust evidence review. Due to the difference between these medicines and their respective disease states, the onset of response on neutrophil count from filgrastim therapy occurs very quickly after administration and thus is routinely measured to ascertain treatment effectiveness. In contrast, there is no such clear-cut marker for assessing the onset of response from infliximab therapy at these very early stages. Hence why an extensive evidence review was conducted prior to switching patients. The comparison between the implementation of these two biosimilars demonstrates that each biosimilar medicine requires a distinct and individualised approach when considering its introduction into the clinical setting; one approach does not suit all.

In the field of gastroenterology, biosimilar adalimumab, which is licensed to treat IBD, was recently granted market authorisation (205). In the Irish context to date, there has been efforts made to introduce or switch patients to this biosimilar (206). In contrast to infliximab, which is commonly dispensed in the secondary care

environment, adalimumab is predominantly dispensed by pharmacists in the primary care setting. This difference is quite interesting as it raises the issue that perhaps primary care pharmacists should be targeted by regulatory agencies to encourage patients to switch to biosimilar adalimumab in an effort to increase biosimilar medicine market penetration. However, as previously noted, this switch would have to be initiated by the prescribing physician (175) and be based upon appropriate evidence. Indeed, there are already many interesting and established approaches to biosimilar medicine implementation which demonstrate that just because a biosimilar medicine is licensed, does not mean that its use will be accepted by prescribers nor that all patients receiving the originator brand should be automatically switched. One such approach is whereby the American National Kidney Foundation sponsored a symposium entitled '*Introduction of Biosimilar Therapeutics Into Nephrology Practice in the United States*' (207). With an anticipated increase in biosimilar products in the field of nephrology, mutually accepted lack of knowledge regarding the biosimilar approval process and development, and lack of trust with respect to biosimilar medicines' safety and efficacy, this community of experts decided to meet at a nationwide level to discuss the introduction of biosimilars into their area of medicine. The colloquium highlighted several controversies but also made recommendations related to public policy, professional and patient education, and research needs (207). With the introduction of new biosimilars set to increase on the market in coming years (208), this example of individual fields of medicine taking responsibility for biosimilar usage pertaining to their area may be a safe, feasible and effective approach to introduce biosimilars into the clinical setting. This strategy might be particularly suitable for fields like oncology and other inflammatory diseases

where biosimilar usage is set to substantially increase (209, 210). Another possible approach is that original biologic and biosimilar medicines can be prescribed on the proviso that patients will be entered in disease-specific registries. These registries may be used as surveillance systems for monitoring ADRs, as well as to quantify and evaluate the risk-benefit ratio throughout a medicinal product's life. Registries may be particularly effective for the evaluation of rare ADRs occurring in the real world population of treated patients, as opposed to the highly selected populations in registration studies (211).

Following on from information released by the medicine management programme (MMP) on biosimilars in the Irish healthcare setting in 2016 (212), and guidance issued by the national cancer control programme (NCCP) on the use of biosimilar medicines in oncology in August 2017 (213), the DoH disseminated a consultation paper in mid-August 2017 (195). This paper indicates that the DoH is developing a national biosimilar medicines policy which aims to increase biosimilar use in Ireland by creating a robust framework where biologicals and biosimilars can be safely, cost-effectively and confidently used in the health service (179). **Table 3.1** reveals which topics of interest are being scrutinised. It is hoped this policy will address the interhospital variation to biosimilar medicine implementation in Ireland and shorten the acceptance process of using biosimilars in the clinical setting. An interesting issue raised by the consultation paper is that of inappropriate business practices (179). Although this was not of concern for this large acute Irish teaching hospital, the impact of the source of information and collaboration of prescribers with the pharmaceutical industry can in principle, have an influence on originator product and biosimilar product prescribing patterns. The consultation paper highlights that France

and Germany have laws banning physicians from receiving gifts from pharmaceutical companies. For biosimilar medicine uptake to increase and be maintained, the information and evidence used by prescribers must not be tainted with commercial interests.

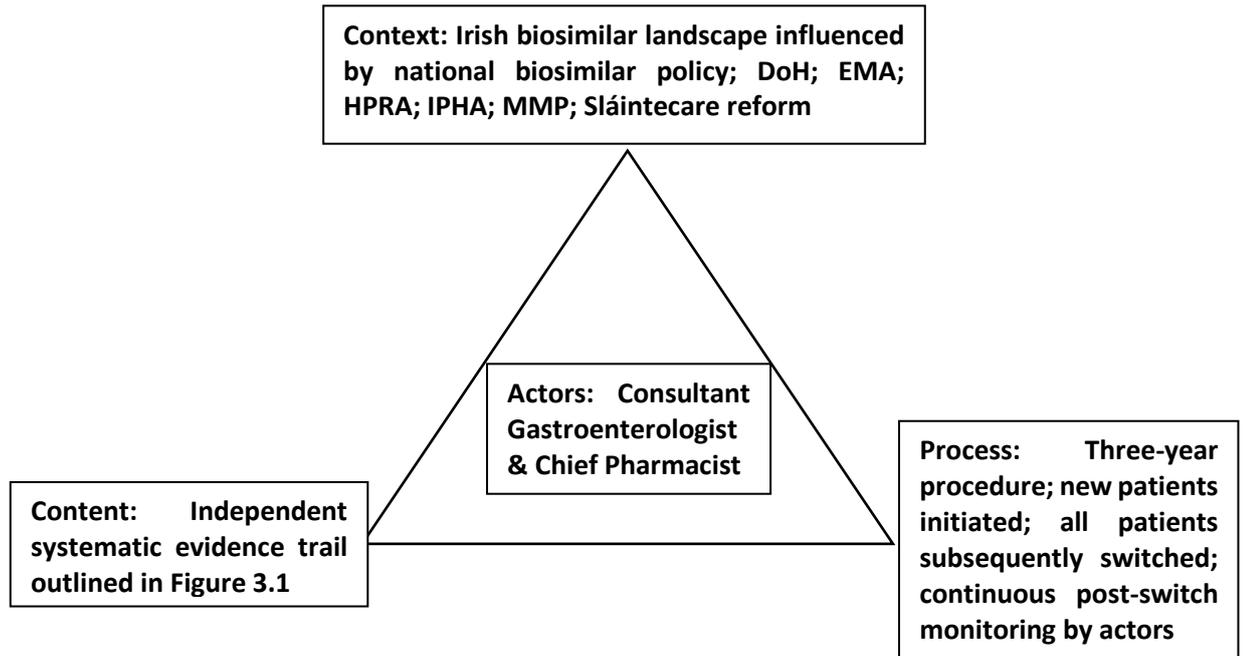
Table 3.1 Topics under investigation in the Irish biosimilar consultation paper

Topic	Description
Prescribing and Interchangeability	By focusing on the remit of biological medicine prescribing, it is hoped that the low uptake of biosimilars in Ireland can be increased
International Biosimilar Medicines Policies	International policies are being examined to decide which policy, if any, could be implemented in the Irish context
Education and Supports	Educational programs and supports are being researched from the perspectives of the patient, healthcare professionals and pharmaceutical suppliers
Incentives and Disincentives	Incentives such as gain-sharing agreements and disincentives like patient co-payment systems are being analysed
Tendering and Pricing Policies	Internal and/or external referencing pricing arrangements as well as the various types of tendering processes used in different countries are being probed for their suitability in the Irish setting
Prevention of Inappropriate Business Practices	In addition to inappropriate business practices previously highlighted, exploration of such professional misconduct is being carried out

One of the consultation paper's recurring themes is that there is too much money being spent on originator biologics when there are cheaper, equally effective alternatives available. It highlights that only 11 biosimilars are currently reimbursable by the Irish healthcare system, while over €200 million is spent each year on biologic

drugs that already have approved biosimilars or that will have available biosimilars throughout 2018 (179). The potential cost savings to be accrued from switching to biosimilars can increase patient access to other new medicinal products. The Irish Pharmaceutical Healthcare Association (IPHA) framework agreement plans to save money on biological medicines (196, 214) where most of these medicines are reimbursed on Ireland's high-tech medicine scheme. This scheme has seen an increase in expenditure from €177.49 million in 2005 to €562.29 million in 2015 (215, 216). This prodigious level of pharmaceutical expenditure cannot be maintained. Research from the Irish National Centre for Pharmacoeconomics (NCPE) has shown that when pharmaceutical companies submit BIAs for new high-cost medicines such as biologics, the majority of these high-cost medicines have a greater cost burden on the budget than what is forecasted in their BIAs (217, 218). This results in taxpayers spending more than anticipated. Thus, an increase in the uptake of biosimilar medicines would be a more sustainable approach to lower the Irish drug bill.

Ireland is currently in the process of attempting to deliver whole system health reform and UHC, known as Sláintecare, for all its citizens over a ten-year period (23). The Sláintecare committee recognises that there is a significant focus on reducing the cost of medicines through the IPHA framework agreement, commercial negotiation with manufacturers supported by health technology assessment from the NCPE, and the development of the national biosimilars policy in draft (21). Through the establishment of a national drugs management portfolio, the Sláintecare committee intend to promote increased use of generic and biosimilar medicines (21). **Figure 3.2** briefly summarises this hospital's biosimilar policy decision using the four components of the HPT framework.



Key: DoH: Department of Health; EMA: European Medicines Agency; HPRA: Health Products Regulatory Authority; IPHA: Irish Pharmaceutical Healthcare Association; MMP; Medicines Management Programme

Figure 3.2 HPT framework describing biosimilar infliximab CT-P13 policy formation and implementation

At present, one approach the DoH could take would be to establish gainsharing agreements at hospital level. Hospitals could be financially awarded for using biosimilars (186) or fiscally penalised for lack of utilisation. Gainsharing agreements have already proven to be a powerful incentive in increasing biosimilar use at EU level (219). With respect to the Danish biosimilar landscape, their initial passive approach to switching actually led to an administrative order (200). Thus, another approach the DoH could adopt would be to introduce reference pricing of biologic products which would accelerate the path to increased biosimilar usage (179). Reference pricing of SMCE medicines has already resulted in savings of millions of euro in the Irish primary care setting (196). Success of the use of biosimilar infliximab CT-P13 at University

Hospital Southampton (220, 221) and in Norway and Denmark was observed, where biosimilar infliximab reached market penetration levels in excess of 90% (as of April 2016) (222). Such uptake resulted in substantial drug acquisition cost savings and subsequently increased patient access to the biosimilar medicine (188, 220). A recent report by QuintilesIMS™ has shown that the entrance of biosimilars into the market increases price competition while also generating price reductions for both biosimilar and reference products (223). However, this report stresses that if the problem of low biosimilar uptake is not appropriately managed in the long term, this could lead to fewer new biosimilars being developed, reducing overall competitive pressure.

3.7 Conclusion

This review examined the evidence considered by a large acute Irish teaching hospital to safely and effectively introduce biosimilar infliximab CT-P13 into the gastroenterology care pathway using components of the HPT framework. There was a significant time lag between regulatory approval and clinical acceptance notwithstanding that the EMA had granted market authorisation for biosimilar infliximab CT-P13 three years prior to the initiation of this hospital's switching process. However, the conservative approach to biosimilar infliximab implementation discussed in the review is justified given the conflicting and changing evidence disseminated from various sources over this three-year period. Alternative approaches that could be used to increase biosimilar medicine adoption into healthcare environments have been suggested. Undisputedly, this review demonstrates that increased biosimilar medicine usage is of benefit to all

stakeholders: increased access for patients, more treatment options for prescribers, sustainable healthcare budgets for payers and more business opportunities for manufacturers.

4 Chapter 4 Cost-effectiveness analysis of a physician-implemented medication screening tool in older hospitalised patients: evidence against policy change at local level

4.1 Chapter description

Similar to chapter 3, a health-related policy decision in a large acute Irish teaching hospital was investigated. However, in this chapter, evidence in the form of an economic evaluation to inform policy process development was synthesised. The policy decision concerned whether a physician would be the most cost-effective healthcare professional to implement a medication screening tool based upon the STOPP/START criteria from the perspective of the Irish health service. A cost-effectiveness analysis alongside conventional outcome analysis in a cluster randomised controlled trial (RCT) was used to generate compelling evidence. The HPT framework was used to describe the different relevant components which show how this topical policy is still maturing. The study applied the policy triangle model to a health-related policy decision made at a local level; this has not been observed in the literature. The other authors of this chapter and publication reviewed the chapter and gave their input and advice during the study. On July 13th, 2018, the following published paper was submitted to the creators of the STOPP/START criteria to help inform future policymaking regarding the most appropriate means of application and delivery for this screening tool.

4.2 Publication

The work of this chapter has been modified and published as O'Brien GL, O'Mahony D, Gillespie P, Mulcahy M, Walshe V, O'Connor MN, O'Sullivan D, Gallagher J, Byrne S, Cost-Effectiveness Analysis of a Physician-Implemented Medication Screening Tool in Older Hospitalised Patients in Ireland, *Drugs & Aging*, 2018, 35(8):751-762, DOI:10.1007/s40266-018-0564-0 (see Appendix VIII for full text).

4.3 Abstract

4.3.1 Background

A recent randomised controlled trial (RCT) conducted in an Irish University teaching hospital that evaluated a physician-implemented medication screening tool demonstrated positive outcomes in terms of reduction of incident adverse drug reactions (ADRs).

4.3.2 Objective

To evaluate the cost-effectiveness of physicians applying this screening tool to older hospitalised patients compared with usual hospital care in the context of the earlier RCT.

4.3.3 Methods

Cost-effectiveness analysis alongside conventional outcome analysis in a cluster RCT. Patients in the intervention arm (n=360) received a multifactorial intervention consisting of medicines reconciliation, communication with patients' senior medical team and generation of a pharmaceutical care plan in addition to usual medical and pharmaceutical care. Control arm patients (n=372) received usual medical and pharmaceutical care only. Incremental cost-effectiveness was examined in terms of costs to the healthcare system and an outcome measure of ADRs during inpatient hospital stay. Uncertainty in the analysis was explored using a cost-effectiveness acceptability curve (CEAC).

4.3.4 Results

On average, the intervention arm was more costly but was also more effective. Compared with usual care (control), the intervention was associated with a non-statistically significant increase of €877 (95% CI –€1,807, €3,561) in mean healthcare cost, and a statistically significant decrease of –0.164 (95% CI –0.257, –0.070) in the mean number of ADR events per patient. The associated incremental cost-effectiveness ratio (ICER) per ADR averted was €5,358. The probability of the intervention being cost-effective at threshold values of €0, €5,000 and €10,000 was 0.236, 0.455 and 0.680 respectively.

4.3.5 Conclusion

Based on the evidence presented, this physician-led intervention is not likely to be cost-effective compared with usual hospital care. More economic analyses of structured medication reviews by other healthcare professionals (HCPs) and by computerised clinical decision support software (CDSS) need to be explored to inform future healthcare policy decisions in this field.

4.4 Introduction

Within the 37 member countries of the OECD, people born today have an average life expectancy of 80.6 years (224). Given this ten-year increase in life expectancy from just 45 years ago, the greatly expanded older person population is one of the most resource-consuming patient groups interfacing with healthcare systems in all OECD countries (225). This cohort is often exposed to inappropriate prescribing and polypharmacy (226, 227) which can frequently lead to ADRs (228, 229). The increasing incidence of ADRs within the older population is a growing health problem (230). It is estimated that approximately 2,000 bed days are due to an ADR at any one time and where the total costs are likely to exceed £171 million annually for ADRs occurring during admission in the UK (231). This cost rises to approximately £1 billion when all ADRs are taken into account (232). Initiatives which enhance medication management in the older people can ameliorate patient outcomes and attenuate unnecessary expenditure (233, 234). Given that an estimated 57% of all ADRs are considered avoidable, it makes sense to invest in interventions to prevent ADRs, particularly in older people who are at highest risk (235).

Structured and unstructured medication reviews in the hospital environment can be an effective means to optimise pharmacotherapy. However, there can be variability in the ways these reviews are implemented (236). They are generally carried out on an *ad hoc* basis and can differ depending on which HCP performs the review (237). The published literature has numerous examples of RCTs testing different interventions that have the common overarching aim of improving prescribing in the older adult (238-240). One trial in particular demonstrated a statistically significant

reduction in serious ADRs (241). However there are only two published clinical trials that have used potentially inappropriate medication (PIM) or potential prescribing omission (PPO) criteria as a structured medication review intervention for the purpose of ADR prevention in high-risk hospitalised older adults (242, 243).

Both of these RCTs have employed the widely used STOPP/START (Screening Tool of Older Persons' Prescriptions / Screening Tool to Alert doctors to Right Treatment) criteria (version 1.0) (244). The fundamental aim of the STOPP criteria is to minimise medication-related adversity by highlighting and avoiding PIMs. The complementary aim of the START criteria is to minimise preventable therapeutic failures by highlighting PPOs and encouraging appropriate prescriptions if they are absent for no justified clinical reason (245). One of these cluster RCTs applied a structured pharmacist review of medication (SPRM) which was supported by a computerised clinical decision support system (CDSS). It resulted in significant reductions of ADRs (243) and proved cost-effective (246).

The other cluster RCT involved a single time-point intervention in which patients had their medications screened according to the STOPP/START criteria by a physician. Instances in which STOPP and START criteria had been contravened were highlighted to the attending medical team with advice to adjust the patients' prescriptions accordingly. This once-off application of STOPP/START criteria alongside usual pharmaceutical care resulted in a significant reduction in incident ADRs compared to similar older patients receiving usual pharmaceutical care only (242). However, before adopting any medication optimisation technology, appraisal of its economic and budgetary impact is important. Notwithstanding the significant ADR attenuation

that arose from the application of the STOPP/START criteria (242), an economic evaluation of this intervention has not yet been undertaken. The aim of this study was to conduct a cost-effectiveness analysis of the physician-implemented structured medication review based on its application in a RCT in an older population that aimed to reduce incident hospital-acquired ADRs. This is the first economic evaluation of a physician-led intervention that is based on the application of the STOPP/START criteria.

The execution of this economic evaluation comes at a time when the Irish healthcare system is undergoing major political, economic and health policy reform under the Sláintecare policy (23). Through political concord, the Irish Government is aiming to establish a universal, single-tier health service where patients are treated solely on the basis of health need but it also plans to reorient the health system *'towards integrated primary and community care, consistent with the highest quality of patient safety in as short a time-frame as possible'* (21). The Sláintecare report states that *'in acute care where hospital assessment is needed, the principal of ambulatory care should apply in order to return older patients to their homes when possible and medically appropriate. The emphasis for these patients should be on ambulatory emergency care, with rapid clinical assessment, investigation and treatment, leading to same day discharge and return to community as the default position'* (21). If demonstrated to be cost-effective, the physician-implemented STOPP/START criteria medication screening tool could prove instrumental in the implementation of certain sub-objectives of the ten-year Sláintecare policy.

4.5 Methods

4.5.1 The prevention of ADRs in older hospitalised patients RCT

Full details of the particular RCT methods are published elsewhere (242, 247). In brief, the single-blinded RCT was conducted in an 810-bed University teaching hospital in the south of Ireland over a 13-month period between May 2011 and May 2012. This trial was cluster-randomised with consultants from each speciality represented in each trial arm. Patients were randomised into either intervention or control groups based on the consultant with primary responsibility for their care during their hospital stay. The intervention arm consisted of 360 patients. The control arm included 372 patients. All in this study received usual medical and pharmacist inpatient care, which consisted of full medication reconciliation, surveillance of prescription order sheets (independent of medical prescribers) with specific written advice attached to the prescription order sheets. The baseline characteristics and trial-related outcomes of the study population are presented (see **Table 4.1**). No significant differences existed between the groups in terms of age, functional status, cognitive function or number of medications at entry to the study (242). Although there was a statistically significant sex imbalance between the groups, it is unlikely that this had a significant influence on the primary outcome results (242, 248).

Table 4.1 Baseline characteristics and trial-related outcomes of study population in the RCT

Variable	Measure	Intervention (n = 360)	Control (n = 372)	P-value
Age	Median (IQR)	80 (73-85)	78 (72-84)	0.100
Male	n (%)	130 (36.1%)	187 (50.3%)	0.001
Female	n (%)	230 (63.9%)	185 (49.7%)	0.001
Nursing home residents	n (%)	51 (14.1%)	36 (9.6%)	0.080
Total number of daily drugs	N	3,147	3,212	0.520
Distribution of drugs	Median (IQR)	9 (6-11)	8 (6-11)	0.710
Length of hospital stay	Median (IQR)	8 (4 – 14)	8 (4 – 14)	0.961
Hospital mortality rate	n (%)	11 (3.1%)	9 (2.4%)	0.535
Key: IQR: Interquartile range; NS: Non-significant (Type 1 error rate of 0.05 used)				

A research physician applied the STOPP/START intervention to patients' medication lists within 48 hours of admission. The intervention consisted of three elements. The first of these involved the research physician applying the STOPP/START criteria once only in each intervention group participant on the basis of the diagnoses documented in their case records and the list of prescribed drugs and doses at the time of study enrolment. The second element involved the research physician discussing the presence of any STOPP/START-defined PIMs and/or PPOs with a senior member of the patient's attending team (i.e. senior residents or in most cases, consultants). Thirdly, within 24 hours of applying STOPP/START criteria, the research physician placed a printed report in the participant's case record, reinforcing the oral recommendations based on the specific criteria that applied in each case. The final

decision regarding acceptance or rejection of STOPP and START criteria recommendations lay with the participant's attending senior medical staff. All patients aged ≥ 65 years admitted under the care of the medical or surgical services through the emergency department were considered eligible for inclusion. However, exclusion criteria were: (i) aged < 65 years, (ii) admission directly to psychiatric services, intensive care unit, palliative care unit, specialist geriatric or clinical pharmacology services, (iii) anticipated length of stay (LOS) < 48 hours, (iv) elective admission, (v) terminal illness, (vi) refusal to participate.

4.5.2 Economic evaluation

The economic evaluation consisted of a trial-based analysis conducted alongside the cluster RCT. The perspective of the Irish public healthcare provider, the HSE, was adopted with respect to trial-related costs and outcomes. Evidence on resource use and patient health outcomes were collected by the research physician during the course of the trial and a retrospective review of patient medical records was carried out. The time horizon for ADR evaluation was confined to patient discharge or ten-day follow-up, whichever was sooner; this was informed by average LOS for an elderly patient in the Irish hospital system at the time (249). The average LOS for patients aged 65 - 74 years is 7.9 days and is 10.4 days for patients aged 75 - 84 years. The study was not designed to measure the medium/long term impact of this intervention and discounting of costs or outcomes was not required due to the limited follow-up period. Moreover, missing/censored data were not an issue in this evaluation, as follow-up was facilitated by a unique hospital number identifier and confined to a single centre over a short time period. Statistical analysis was

conducted on an intention to treat basis, and in accordance with guidelines for conducting economic evaluations alongside cluster RCTs (250), which require that both the correlation and clustering of the cost and effect data be explicitly considered.

4.5.2.1 Cost analysis

Multiple cost components were included in the analysis and are described (see **Table 4.2**). Costs are expressed in Euros (€) using 2012 prices (unless otherwise stated). The primary component was the cost of employing the research physician, who then held the post of specialist registrar (i.e. senior resident) physician in geriatric medicine, to implement the required intervention steps. The mid-point of the HSE specialist registrar physician pay scale was used and adjusted according to guidelines for conducting economic evaluation in Ireland (60, 251). Salary was adjusted for employers' insurance cost, pension payments and general overheads. Based on experience-based opinion from the primary research team and estimates from the literature (252), it was assumed for the analysis that 40 minutes was an appropriate duration to assign for the trained research physician to apply the intervention.

The second component consisted of the associated follow-up time for senior members of patients' attending teams to discuss and decide upon the suggested STOPP/START recommendations. Based on experience-based opinion from the primary research team, it was assumed for the analysis that this took seven minutes. The mid-point on the HSE consultant physician pay scale was used in the cost analysis. The third major component was the cost of hospital inpatient stay; this cost was obtained from aggregated national data (253). In general, micro-costing estimates for

patients are preferable. However, in the context of this piece of research, the 24-hour national Irish hospital stay average cost per patient was more pragmatic to use despite patients being admitted with a diverse range of primary indications. The fourth component consisted of the specialist registrar's training in the use of STOPP/START criteria. Interactive training courses given by the creators of the STOPP/START criteria generally last for approximately four hours and were costed accordingly.

All resource use was valued using a vector of unit cost data presented in 2012 Euro (€) prices and summed to calculate a total cost variable for the statistical analysis given that the trial was completed in 2012. However, at the time of study execution (December 2017), the contemporaneously available healthcare costs (CAHC) in the Irish context were re-applied to the intervention steps. These costs are expressed in 2015 Euros (€) prices unless otherwise stated (see **Appendix IX**). The incremental cost-effectiveness analysis was re-run with the CAHC and original trial effectiveness data (see **Appendix X**). This supplementary analysis was undertaken as a point of interest to examine the stability of medical inflation in Ireland during the post financial crisis period.

Table 4.2 Costs associated with care of patients in intervention arm in 2012

Cost Component	Unit Cost (€)	Description	Reference
Training of research physician in intervention criteria (once-off)	0.56	Circa 240 minutes of training required costing approximately €200.00	Experience-based opinion from primary research team
Research physician applying the intervention	2.50	Median time of three minutes to apply intervention (252)	HSE salary scales (251)
Research physician informing specialist consultant of intervention findings and answering related questions	5.83	Approximated time of seven minutes (Experience-based opinion from original research team)	HSE salary scales (251)
Specialist consultant being made aware and possibly implementing intervention findings	16.33	Approximated time of seven minutes (Experience-based opinion from original research team)	HSE salary scales (251)
Research physician compiling printed report of intervention findings	25.00	Approximated time of 30 minutes (Experience-based opinion from original research team)	HSE salary scales (251)
Hospitalisation costs	820.00	24-hour national Irish hospital stay average cost per patient	Healthcare Pricing Office (253)
Key: HSE: Health Service Executive			

4.5.2.2 Effectiveness analysis

The primary outcome measure of this cluster RCT was the difference in the proportion of participants in the two arms experiencing one or more ADRs during index hospitalisation. ADRs were identified by the research physician and a blinded second researcher. A comprehensive description of ADR identification and outcomes is provided elsewhere (242).

4.5.2.3 Cost-effectiveness analysis

In an economic evaluation, one health technology (treatment/intervention) is considered more cost-effective than its comparator if it meets one of the following criteria (54);

- a) Less costly and more effective;
- b) More costly but more effective, with an incremental cost-effectiveness ratio (ICER) which is considered acceptable by decision-makers;
- c) Less costly and less effective, but the additional cost per unit of effect of its comparator is not considered worth paying by decision-makers.

In the context of the current study, a cost-effectiveness analysis was conducted to identify which of the three conditions applies here. Notably, the ICER represents the additional cost per unit effect, which in this case, is the additional cost of preventing an additional non-trivial ADR in secondary care. This raises the concern of what healthcare policymakers and decision-makers in Ireland would be willing to pay to prevent an ADR. While threshold values exist for some generic measures such as quality-adjusted life years (QALYs), no such value per ADR prevented currently exists. In this analysis, we present our results in the context of a number of hypothetical

thresholds, as previously proposed in the literature (246). Recent work that compares methods for estimating direct costs of ADRs may inform a threshold value for ADR prevention in the future (254).

Statistical techniques were adopted to account for the effect of both clustering and correlation of cost and effect data collected alongside cluster RCTs (255). The incremental analysis was undertaken using multilevel regression models for both the cost and effect data. Both models were estimated to control for treatment arm, age, sex, number of medications at admission and consultant (cluster group). The regression for total cost variable was estimated using a multilevel mixed-effects linear regression model and the regression for the ADR event variable was estimated using a mixed-effects logistic regression model. The estimated treatment arm effects represent the incremental costs and incremental effects for the intervention relative to the control. The 95% confidence intervals report the statistical significance of these co-efficients based on standard errors estimated using the '*mixed*' command in STATA® version 13 (StataCorp, College Station, TX, USA).

Uncertainty in the analysis was addressed by estimating confidence intervals and a cost-effectiveness acceptability curve (CEAC), which links the probability of a treatment being cost-effective to a range of potential threshold values (λ) that the healthcare system may be willing to pay for an additional unit of effect (256). Commonly, non-parametric bootstrapping can be conducted on the difference in mean costs and mean ADRs to generate ICER replicates with which to construct a CEAC (257). However, the CEAC in this analysis was estimated parametrically using the net benefit regression framework following the method proposed by Hoch *et al.*

(258). The CEAC explicitly presents the uncertainty relating to the threshold value coupled with the statistical variability inherent in trial data.

Finally, a series of scenario analyses was performed which varied the time required by all HCPs to complete the intervention by +/- 50%. The scenario analysis was re-run using CAHC and the original trial effectiveness data (see **Appendix XI**). The aim was to assess the cost-effectiveness of this intervention if it was to be implemented in usual clinical care by hospitals in more recent times. Analysis was performed using STATA® version 13 and Microsoft Excel® 2010 (Microsoft Corporation, Redmond, WA, USA).

4.5.3 Guidelines and ethical considerations

This analysis followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines for reporting health economic evaluations (259) (see **Appendix XII**) with joint reference to the published good research practices for cost-effectiveness analysis alongside clinical trials, i.e. the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Good Research Practices: Randomized Clinical Trials-Cost-Effectiveness Analysis (ISPOR RCT-CEA) report (260). The original clinical cluster randomised trial conformed to Consolidated Standards of Reporting Trials (CONSORT) guidelines (261). The research ethics committee (institutional review board) of the local teaching hospitals network approved the trial protocol and the trial was registered with the United States National Institutes of Health (NCT01467050-<http://clinicaltrials.gov/show/NCT01467050>). Written consent was sought and obtained from all participating patients, prior to enrolment in the original cluster RCT

study. Ethical approval was not required for this secondary analysis of anonymised data.

4.6 Results

The physician-led STOPP/START intervention resulted in a marked absolute risk and relative risk reduction for incident ADRs i.e. 11.4% and 47.7% respectively (242). However, this was accompanied by an increased cost relative to usual medical and pharmaceutical care (**Table 4.3**). The mean (standard deviation (SD)) cost of caring for an intervention patient during a single admission was €12,102 (€13,490). In the control group, the mean (SD) cost of care was €11,160 (€12,506). Median costs were higher for the intervention group (€7,430) compared to the control group (€7,380). Following application of a multi-level mixed effects model in STATA[®] version 13 and accounting for baseline differences across both arms, the adjusted incremental difference in cost of €877 was statistically non-significant.

In contrast, the effectiveness measures favoured the intervention strategy and were statistically significant. The odds ratio for a patient experiencing an ADR was 0.391 when comparing the intervention (STOPP/START criteria) group to the control (usual hospital care) group. This related to an adjusted difference in the mean number of ADRs of -0.164. Although the physician-implemented STOPP/START intervention was more costly, it too was more effective than usual clinical care. The calculated ICER was €5,358 for the prevention of an ADR. However, as with all attempts to calculate the cost-effectiveness of an intervention, there is a degree of uncertainty surrounding the ICER. Even if the healthcare payer was willing to pay the €5,358 for

the prevention of an ADR, the probability of the intervention being cost-effective was 50%. There was a 92.6% probability that the intervention would be cost-effective if the healthcare payer was willing to pay €20,000 for the prevention of an ADR (**Table 4.3** and **Figure 4.1**). When the cost-effectiveness analysis was rerun using CAHC and the original trial effectiveness data, the ICER underwent a slight increase to €5,469 (see **Appendix X**). Scenario analyses demonstrated that if HCP times associated with the intervention were altered by +/- 50%, this had a minimal effect on the original ICER estimate (**Table 4.4**). This was also true of the scenario analyses that used CAHC and original trial effectiveness data (see **Appendix XI**).

The overall cost of applying the STOPP/START intervention to a group of 360 patients was estimated to be approximately €18,000 or €50 per patient. The majority of the intervention costs were associated with the expense of the research physician's time conducting the intervention (~€33 per patient). Length of hospital stay was responsible for most of the cost associated with management in both arms of the cluster RCT.

Table 4.3 Incremental cost-effectiveness analysis using 2012 data

	Intervention group (n = 360)	Control group (n = 372)
Cost analysis		
Total healthcare cost (€)		
Mean (SD)	12,102 (13,490)	11,160 (12,506)
Effectiveness analysis		
Participants experiencing ≥ 1 ADRs [n (%)]	42 (11.67)	78 (20.97)
ADRs experienced per patient [n (%)]		
0	318 (88.33)	294 (79.03)
1	39 (10.83)	67 (18.01)
2	3 (0.83)	11 (2.96)
ADRs per patient [mean (SD)]	0.125 (0.356)	0.239 (0.492)
Incremental cost-effectiveness analysis	Intervention vs Control	
Incremental cost		
Difference in mean healthcare cost (€) ^(a,b)	877 (95% CI -1807, 3561)	
Incremental effect		
Difference in odds ratio for ADR events ^(a,c)	0.391 (95% CI 0.233, 0.657)	
Difference in mean ADR events ^(a,c)	-0.164 (95% CI -0.257, -0.070)	
ICER per ADR averted (€)	5,358	
Threshold value (λ) per ADR averted (€)	Probability that intervention is cost-effective ^(d)	
0	0.236	
500	0.255	
1,000	0.275	
5,000	0.455	

Threshold value (λ) per ADR averted (€)	Probability that intervention is cost-effective ^(d)
10,000	0.680
20,000	0.926

Key: SD: standard deviation; ADR: adverse drug reaction; CI: confidence interval; ICER: incremental cost-effectiveness ratio

- a) Reported estimates for incremental differences in costs and effects adjusted to account for baseline differences between arms.
- b) Regression for total costs estimated using multilevel mixed-effects linear regression models and controlling for treatment arm, age, sex, number of medications at admission and clustering.
- c) Regression for ADR event estimated using mixed effect logistic regression models and controlling for treatment arm, age, sex, number of medications at admission and clustering.
- d) Probabilities for cost-effectiveness estimated parametrically using net benefit regression models for analysis at each threshold value.

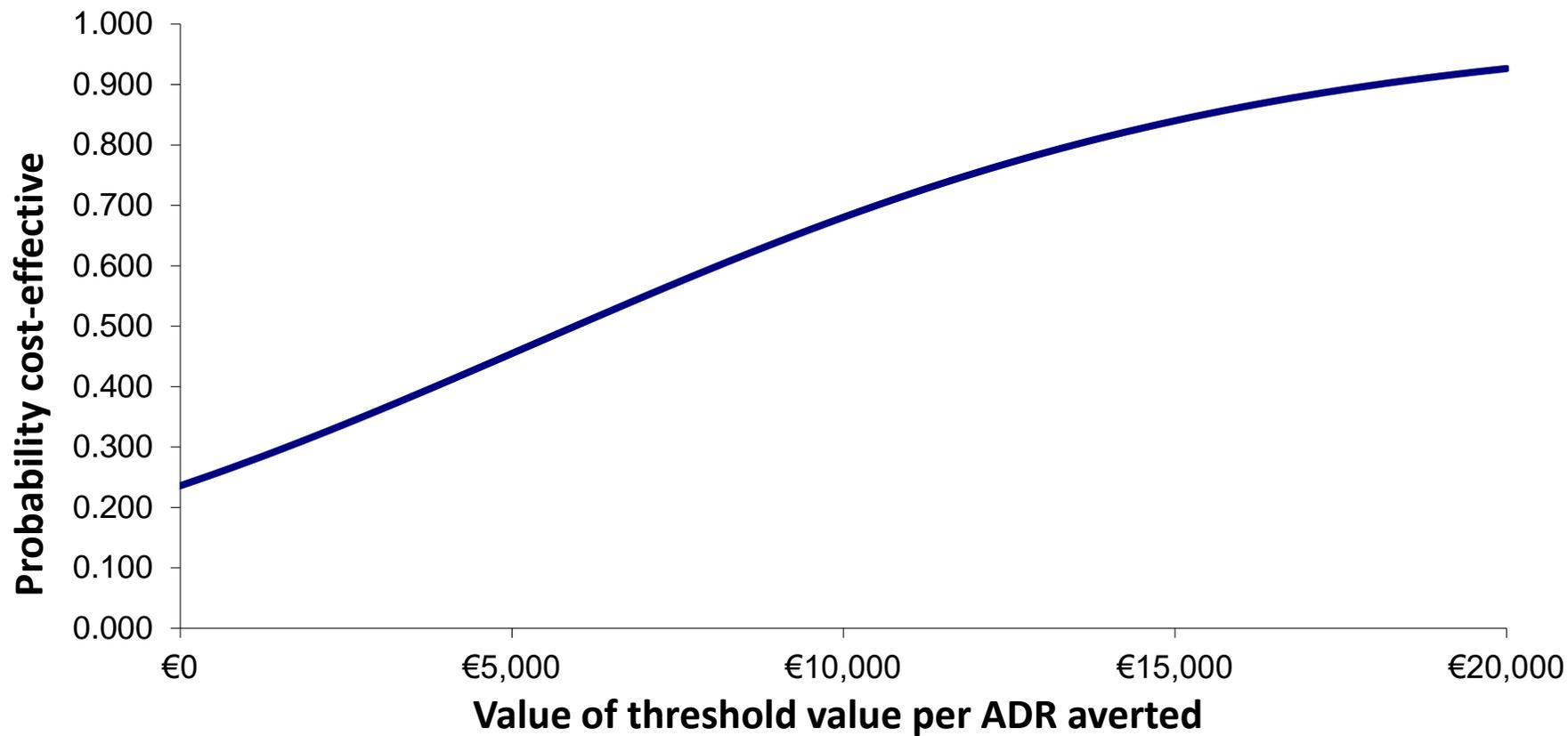


Figure 4.1 Cost-effectiveness acceptability curve (controlling for treatment arm, age, sex, number of medications at admission and consultant (cluster group))

Table 4.4 Scenario analysis using 2012 data

50% increase in healthcare professional time	Incremental Analysis - Intervention vs Control
Incremental Cost: Total Cost (€) <i>Difference in Mean</i>	900 (95% CI -1783, 3584)
Incremental Effect: No. of ADR Events (n) <i>Difference in Mean</i>	-0.164 (95% CI -0.257, -0.070)
Incremental cost-effectiveness ratio (€)	5,500
50% decrease in healthcare professional time	Incremental Analysis - Intervention vs Control
Incremental Cost: Total Cost (€) <i>Difference in Mean</i>	854 (95% CI -1831, 3539)
Incremental Effect: No. of ADR Events (n) <i>Difference in Mean</i>	-0.164 (95% CI -0.257, -0.070)
Incremental cost-effectiveness ratio (€)	5,216
Key: ADR: adverse drug reaction; CI: confidence interval	

4.7 Discussion

It is unlikely that the physician-led STOPP/START intervention is cost-effective. For instance, at a willingness-to-pay threshold of €10,000 per ADR averted; the probability of the intervention being cost-effective is only 68%. The probability of the intervention being cost-effective increases to 92.6% if a significantly higher threshold of €20,000 is applied. The willingness-to-pay thresholds used in this analysis were arbitrary but when one considers that the mean cost associated with a single ADR event in secondary care has been estimated at €2,250 (262), the threshold values presented in **Table 4.3** and **Figure 4.1** are a reasonable measure of what could be considered value for money. This cited mean cost of a single ADR also suggests that

it is unlikely decision-makers would be willing to pay the quoted threshold values because a high probability of cost-effectiveness is only reached at high threshold values. Similar increases in the cost of care could be imputed from this study, as patients who experienced an ADR had their median LOS increased by three days (242).

The principal barrier to the application of this intervention by a trained physician at a wider level is physician working hours' capacity. The senior resident research physician screened no more than four new patients each day for trial enrolment during the cluster RCT. It should be noted that the research physician was not employed on a full-time basis to apply the intervention to patients. If all older hospitalised patients were to receive this level of pharmaceutical care, increased staff numbers would likely be required. However, given the results from the analysis, it could be argued that the role of the specialist physician is to conduct all relevant medical duties in the secondary care environment. Although there are some published data in the primary care setting literature (263), we could find no reputable references dealing with economic analyses of physician-led medication-related interventions in the secondary care setting literature. Thus, it is difficult to align the results of this analysis with similar studies. One similar trial involving a research pharmacist conducting a similar medication review-based intervention supported by computerised CDSS proved to be cost-effective relative to routine hospital care (246). A recent systematic review investigating the effectiveness and cost-effectiveness of interventions aimed at preventing medication error (medicines reconciliation) at hospital admission demonstrated that the majority of these interventions are pharmacist-led, not physician-led (264) and that the pharmacist-led interventions are

generally considered more cost-effective than the respective study comparator (265). In addition, two ongoing European multi-centre randomised clinical trials i.e. SENATOR and OPERAM (266-268) implement the STOPP/START criteria using a computerised CDSS. A recent systematic review concluded that computerised interventions are associated with a significant reduction in potentially inappropriate prescribing (PIP) in older hospitalised patients (269). Computerised interventions in this field appear to reduce cost (270) and be cost-effective (271). It is also envisaged that the application of STOPP/START criteria in the SENATOR and OPERAM trials may prove less labour-intensive and more cost-effective than its application in the RCT analysed in this study (272). Given all this evidence, it is likely that the more clinically effective and cost-effective medication screening interventions in older hospitalised patients in the future will comprise of pharmacist-led and/or computerised CDSS interventions.

A study conducted in Canada assessed the cost-effectiveness of self-managed versus physician-managed oral anticoagulant therapy over a 5-year period using a Bayesian Markov model (273). Self-management resulted in fewer adverse drug events than physician management with the average discounted incremental cost of self-management relative to physician management calculated to be \$989 per patient with incremental QALYs of 0.07 gained (273). Although this study did not assess medication screening in the elderly *per se*, it is yet another example of where a physician-implemented medication intervention was not found to be cost-effective. Conversely, the literature once again appears to favour medication screening programmes involving or implemented by pharmacists. This point is supported by

two recently published studies demonstrating cost-effectiveness of pharmacist-driven medication reviews towards optimisation in older patients (238, 274).

Notwithstanding the research physician's absence during medical rounds, the 83.4% acceptance rate of STOPP/START recommendations by attending doctors is noteworthy (242). However, in a very similar analysis where the research pharmacist was absent during medical rounds, a lower acceptance rate of 38.5% by attending doctors was notable (275). As the present analysis argues that pharmacist-led medication screening interventions are an effective and a cost-effective solution, the low rate of acceptance of pharmacist prescribing recommendations by attending physicians needs to be further investigated. In relation to pharmacist medication reviews, a robust method for economic evaluation of such medication assessments has been elucidated (276). Ideally, the evaluation should be conducted with a 1-year follow-up period from a healthcare service provider viewpoint. Health-related quality of life (HRQoL) is contended as the preferred effectiveness measure utilised, allowing correlation with confirmed societal values. The ultimate and most comprehensive appraisal would be a cost-benefit evaluation over a 5-year period from a societal perspective. Thus, if the standard practice model of medication reviews is to be pharmacist-led, the economic evaluation aspect of such reviews should be conducted using the proposed methods.

The cluster randomisation of the RCT that this evaluation is based upon resulted in a statistically significant sex imbalance between the control and intervention groups (significantly fewer women in the control group (49.7%) than in the intervention group (63.9%)). Although sex imbalance in any RCT is not desirable, there is no

evidence to indicate that sex had a significant influence on the prevalence rates of PIMs, PPOs, or incident ADRs in the trial. The literature has shown that females experience higher rates of PIMs and ADRs relative to males (277-279). Given the higher proportion of women in the intervention group, one would have expected higher rates of ADRs in this arm, yet the results demonstrated the contrary. Therefore, it is unlikely that the sex imbalance between groups had a significant influence on primary outcome trial results. There were no other significant demographic differences between the two treatment arms. As stated, demographic analysis is presented in the original RCT paper (242).

It has been established that conducting economic evaluations based on data from RCTs is a suitable methodology (280). This approach has two main advantages i.e. (i) internal validity is maintained due to the comprehensive nature of data collection during the trial and (ii) there is a modest marginal cost associated with collecting required data from a trial which is predominantly clinically orientated (280). While a cost-utility analysis with a health-related outcome measure is recommended as the reference case in the Republic of Ireland (60), it was not a realistic outcome measure for this analysis. The population under consideration had multiple co-morbidities and often an initially poor health status (242). Therefore, HRQoL was not appropriate in this case (281). Appropriate methods were used to investigate the cost-effectiveness analysis of the trial data. Multi-level mixed effect models were chosen as they are an acceptable means for estimating the incremental net benefits for a clinical trial of this nature. Clustered data can potentially lead to biased results (282). Normal statistical analyses are generally inappropriate, however the methods employed for our

analysis surmounted this issue (255). These techniques account for both the clustering and correlation of cost and effect data.

4.7.1 Limitations

There are several limitations to this economic evaluation, principally pertaining to extrapolation of the findings to routine clinical practice. Training costs and time estimates were not recorded at time of event and were retrospectively informed by the primary research team. It is likely that some costs associated with this intervention may have been overestimated or underestimated. For example, the seven-minute time period allocated for discussion of STOPP/START recommendations could vary considerably depending on the number of recommendations generated and the subjective prescribing assessment thought processes of the attending consultant. In addition, the 30-minute time period allocated to compiling the research physician's printed report could be replaced by a five-minute handwritten summary of recommendations into patients' medical records. However, the scenario analysis demonstrated that if HCP time associated with intervention implementation was altered by 50% in both directions, this had a minimal effect on the original ICER estimate (see **Table 4.4**). Furthermore, a time and motion study, which gathers data on HCP time required to complete the intervention, would have reduced uncertainty surrounding this input. As HCPs become more familiar with the application of the STOPP/START criteria, they will be able to apply them more effectively and arrive at decisions at a faster rate.

ADRs are often compared to icebergs (283); those that are visible and identified, and those that are below the water's surface where neither patient nor intervening

clinician recognise that they are drug effects, and thus unquantifiable. Therefore, it is possible that the amount of ADRs identified in both arms of the trial is not the true value. Depending on the type and severity of ADR, the cost, patient LOS, and overall impact on healthcare utilisation, can vary dramatically (262, 284). This level of detail was not reflected in our evaluation. Therefore, it is potentially dangerous to dismiss the intervention as not being cost-effective because the outcome at the time was not measurable or identifiable. There are also those that may be causing no symptoms or signs at the time but represent a real risk in the future. Ideally, a longer duration of follow-up for ADR evaluation would have been preferable as it possibly could have allowed for further identification of ADRs.

Moreover, this evaluation is based on the work of one research physician in a single centre. Aspects of the intervention that would be variable between sites include the clinical experience of the research physician involved and the extent of the uptake of STOPP/START criteria recommendations by the receiving medical team. The attending physician is solely responsible for deciding whether the application of the STOPP/START criteria is clinically important or not. This is a subjective choice, irrespective of formal training. There are other examples of medication optimisation due to the application of the STOPP/START screening tool (245). This single study site increased the possibility of crossover learning between healthcare colleagues within the secondary care environment. However, if healthcare decision-makers are insistent about supporting and promoting physician-led medication screening interventions, this evaluation should be carried out on a larger scale involving multiple hospital sites as is the case with the SENATOR and OPERAM clinical trials (266-268).

4.7.2 From evidence to policy

As stated, the trial was conducted in 2011/2012 and cost-effectiveness was calculated using 2012 healthcare costs. When the analysis was re-run using CAHC and original trial effectiveness data, the cost of the intervention was marginally lower (see **Appendix IX**); however, there was a slight ICER increase which is attributed to the increased 24-hour national Irish hospital stay average cost per patient (see **Appendix X**). It is unlikely that hospital decision-makers would execute the rollout of this intervention today as it has become less cost-effective in recent times. However, a BIA would have to be completed alongside the cost-effectiveness analysis to assess if hospital decision-makers and other policymakers were serious about its adoption (285). In addition, the results of economic analyses based on RCTs must be interpreted with caution especially if there are limitations or flaws inherent in trial design. However, the RCT that formed the basis of the present cost-effectiveness analysis achieved 80% power to detect a statistically significant difference in ADR incidence between the groups at the 95% confidence level (242). It would have been interesting to calculate the incremental net benefit statistic to derive the same conclusion on cost-effectiveness like that of the ICER. This was not possible since a willingness-to-pay threshold for ADRs has not yet been elucidated.

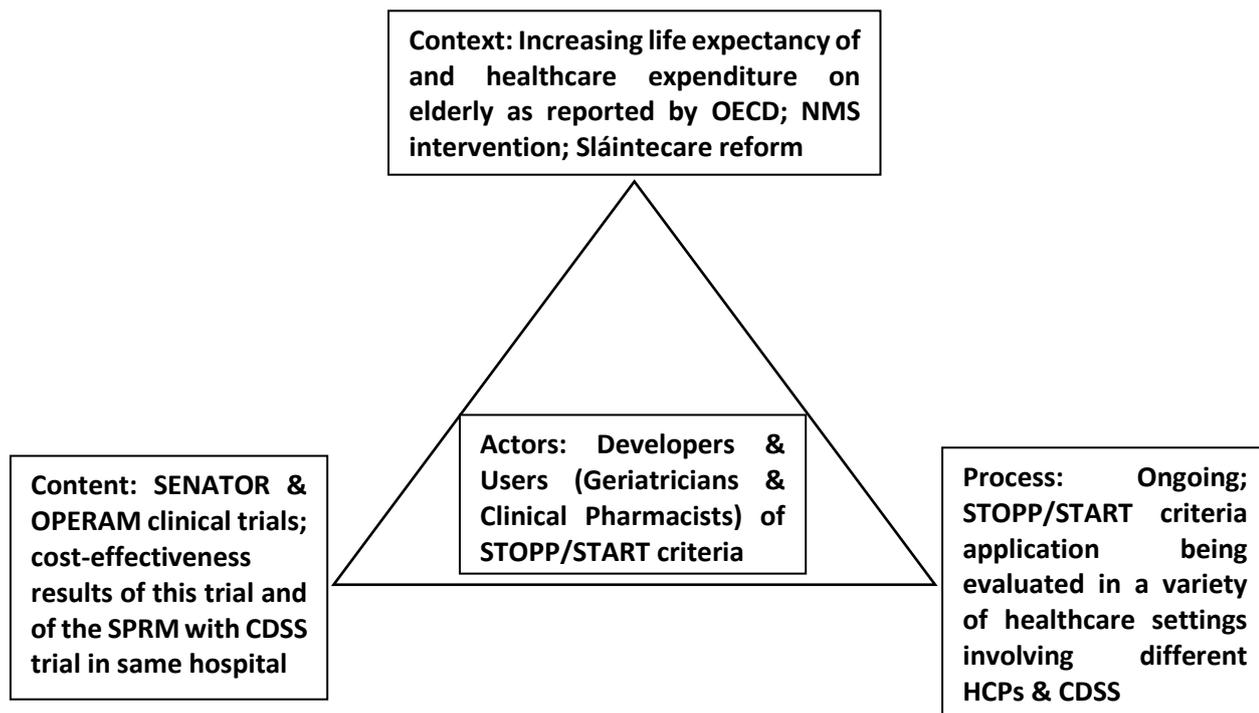
This is the first study to evaluate the economic impact of a physician-led medication review intervention based upon the STOPP/START criteria where recommendations from the CHEERS statement were implemented to ensure that this analysis presents a transparent high-quality evaluation. Since their development in 2008 (244), the STOPP/START criteria have become an extensively used method of identifying and

improving instances of PIP (275, 286). This analysis provides further information about the adoption of the STOPP/START guidelines as a fundamental part of any healthcare review conducted by a HCP in an older population.

STOPP/START creators Professor Stephen Byrne, Professor Denis O'Mahony, and Dr. Paul Gallagher (287) of Schools of Pharmacy and Medicine, University College Cork (UCC), Ireland are currently updating the STOPP/START guidelines (version 3.0). This revision is scheduled to be released during the summer of 2021. In this study, the application of the STOPP/START criteria did not demonstrate cost-effectiveness in the secondary care setting. In line with the Sláintecare aim of reorienting health services towards integrated primary and community care (23), the formal use of the STOPP/START criteria (version 3.0) by pharmacists and GPs in primary care may prove cost-effective for the health system and wider society. Further research is required on its application in this setting, but research shows that addressing a subset of chronic illnesses and related medications, including congestive heart failure, diabetes, asthma, angina, epilepsy and hypertension, through clinical leadership in primary care settings, results in better outcomes and more appropriate care than if provided in hospital (21). When these conditions are effectively managed by primary care teams and patients themselves are empowered, exacerbations or hospitalisations can be minimised (288). The impact for patients is better health when chronic conditions do not deteriorate and for health systems the cost savings are significant (289). In addition, the Irish Pharmacy Union (IPU) conducted a new medicines service (NMS) pilot in Ireland throughout 2017. This pilot demonstrated that the community pharmacist-led NMS intervention had benefits for the vast majority of patients, with a positive effect on a total of 85% of all patients in the

treatment arm (290). Already, the English NMS has proven to be cost-effective compared with normal practice (291). The cost-effectiveness must still be evaluated for the IPU NMS. However, if proven, the STOPP/START creators plan to engage in talks with the IPU on integrating the STOPP/START criteria into the IPU NMS intervention. Thus, the formal transposition of the revised criteria to primary care settings is being considered by the STOPP/START actors at present.

Another avenue the STOPP/START creators are exploring is that the criteria would be exclusively applied by pharmacists in association with a computerised CDSS in the healthcare setting as opposed to by physicians. As mentioned, a recent cluster RCT conducted in the same 810-bed University teaching hospital applied a SPRM which was supported by a computerised CDSS. It resulted in significant reductions of ADRs (243) and proved cost-effective (246). Reducing the involvement of the physician in such interventions would improve the cost-effectiveness from a healthcare payer perspective. The STOPP/START creators are involved in both SENATOR and OPERAM trials. These trials are currently reporting on similar interventions where the STOPP/START criteria are being implemented via a computerised CDSS with additional pharmacist involvement. To date, the policy process on how the STOPP/START criteria should be optimally delivered (by who, what setting, what type of software etc.) is still growing. **Figure 4.2** briefly summarises the content, context and process underpinning this evolving policy decision using the HPT framework thus far (46).



Key: CDSS: Clinical Decision Support Software; HCP: Healthcare Professional; NMS: New Medicines Service; OECD: Organisation for Economic Co-operation and Development; SPRM: Structured Pharmacist Review of Medication

Figure 4.2 Walt and Gilson policy triangle model describing STOPP/START criteria policy formation, growth and evaluation

4.8 Conclusion

Based on the information extracted from the cluster RCT, the physician-implemented medication screening tool based on the STOPP/START criteria is unlikely to be considered cost-effective. The healthcare payer would have to pay €20,000 to attain a 92.6% probability that this intervention, which prevents ADRs, is cost-effective. However, as the authors are unaware of decisions previously made based on the cost per ADR prevented, there is uncertainty regarding the cost-effectiveness status of the intervention from a policy perspective. Moreover, while the difference in incremental effects on an individual basis did demonstrate statistical significance, the difference

in overall incremental costs did not. To date, the literature appears to be sparse with regard to physician-implemented medication review interventions in the secondary care setting in contrast with the multiplicity of studies describing pharmacist-led programmes that appear to be clinically effective and budget positive (265). At a minimum and as portrayed by the HPT framework, this evaluation further adds to the growing body of evidence that a structured form of medication review and reconciliation incorporating STOPP/START criteria is superior to usual clinical practice. The present data suggests that a pharmacist with/without computerised CDSS designed for STOPP/START criteria employed to carry out such medication reviews may be a more cost-effective approach than a medication review provided by a specialist physician.

5 Chapter 5 Cost minimisation analysis of intravenous and subcutaneous trastuzumab treatment in patients with HER2-positive breast cancer: evidence for policy change at regional level

5.1 Chapter description

Similar to chapters 3 and 4, a health-related policy decision was investigated. This time the setting grew to include two large acute University teaching hospitals within the south/south west hospital group in Ireland. Like in chapter 4, evidence in the form of an economic evaluation to inform policy process development was synthesised. The policy decision concerned whether trastuzumab subcutaneous treatment should replace trastuzumab intravenous treatment for HER2-positive breast cancer patients in routine clinical practice. A prospective observational study in the form of a cost minimisation analysis constituted study design and was used to generate compelling evidence to support policy change. The HPT framework was used to describe the various contributing components which show how this contemporary policy is still evolving. The study applied the policy triangle model to a health-related policy decision made at a provincial/regional level; this has not been observed in the literature. The other authors of this chapter and publication reviewed the chapter and gave their input and advice during the study. On September 25th, 2018, at the request of its Chief Pharmacist, the following published paper was submitted to the

HSE-National Cancer Control Programme to inform policymaking and reimbursement on this topic.

5.2 Publication

The work of this chapter has been modified and published as O'Brien GL, O'Mahony C, Cooke K, Kinneally A, Sinnott SJ, Walshe V, Mulcahy M, Byrne S, Cost Minimisation Analysis of Intravenous or Subcutaneous Trastuzumab Treatment in Patients with HER2-Positive Breast Cancer in Ireland, *Clinical Breast Cancer*, 2019, 19(3):e440-e451, DOI:10.1016/j.clbc.2019.01.011 (see Appendix XIII for full text).

5.3 Abstract

5.3.1 Background

Two large acute Irish University teaching hospitals changed the manner in which they treated human epidermal growth factor receptor (HER)2-positive breast cancer patients by administering trastuzumab via the subcutaneous (SC) route into their clinical practice.

5.3.2 Objective

To compare the trastuzumab SC and trastuzumab intravenous (IV) treatment pathways in both hospitals and assess which route is more cost-effective and time saving in relation to active healthcare professional (HCP) time.

5.3.3 Methods

A prospective observational study in the form of cost minimisation analysis constituted the study design. Active HCP time for trastuzumab SC and IV-related tasks were recorded. Staff costs were calculated using fully loaded salary costs. Loss of productivity costs for patients were calculated using the human capital method.

5.3.4 Results

On average, the total HCP time saved per trastuzumab SC treatment cycle relative to trastuzumab IV treatment cycle was 59.21 minutes. Time savings in favour of trastuzumab SC resulted from quicker drug reconstitution, no IV catheter installation/removal, and less HCP monitoring. Over a full treatment course of 17 cycles, average HCP time saved accumulated to 16.78 hours with an estimated direct

cost saving of €1,609.99. Loss of productivity for patients receiving trastuzumab SC (0.60 days) was less than that of trastuzumab IV (2.15 days) for a full treatment course.

5.3.5 Conclusion

Trastuzumab SC treatment has proven to be a more cost-effective option than trastuzumab IV treatment that also generated greater HCP time savings in both study sites. Healthcare policymakers should consider replacing trastuzumab IV with trastuzumab SC treatment in all eligible patients.

5.4 Introduction

Breast cancer is the most common cancer in women (292, 293). The humanised monoclonal antibody trastuzumab is indicated for the treatment of both early and metastatic human epidermal growth factor receptor (HER)2-positive breast cancer (294). In this group of patients, trastuzumab is administered every three weeks for one year (either 17 or 18 treatment cycles depending on the decision of the attending physician) in early breast cancer or, in the case of metastatic breast cancer until disease progression, by intravenous (IV) infusion at a dose calculated according to the patient's weight (294). The duration of administration for trastuzumab IV in this condition is 90 minutes in the first administration (loading dose) and 30 minutes for consecutive treatment administrations (maintenance dose) (294). In addition to the IV formulation, a subcutaneous (SC) formulation exists. It has an administration time of less than five minutes and is given by a single-use injection device (SID) or via handheld syringe. The dose is independent of the patient's weight. The SC formulation has demonstrated pharmacokinetics, efficacy, and a safety profile comparable to the IV formulation in patients with early HER2-positive breast cancer in the enHANced treatment with NeoAdjuvant Herceptin (HannaH) trial (295). Both the safety and tolerability of Subcutaneous trastuzumab for the adjuvant treatment of Human epidermal growth factor receptor 2-positive early breast cancer (SafeHer) trial and the Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHer) trial have also corroborated these findings (296, 297).

There are two general approaches to costing healthcare: top-down and bottom-up. A top-down approach estimates the cost of an individual service on average, usually using routinely available data e.g. average per diem costs. Top-down costing studies tend to be relatively quick and straightforward to conduct. However they are also less precise and cannot provide information on individual factors driving the costs (54). Disease-specific per diem costs (or daily cost) give the average daily cost for treatments in each disease category but may still be quite broad (54). Case-mix groups yield the costs for each category of 'case' or hospital patient and take length of stay into account. While this approach to costing is more precise than the aforementioned approaches, a bottom-up approach (micro-costing) generates a more precise estimate but is more onerous to perform. In micro-costing, all resources used are identified where the unit costs of the resources are multiplied by the quantities used (54). Studies examining the differences between the cost estimates produced by both top-down and bottom-up approaches have concluded that bottom-up approaches are preferable for estimating cost components which have a large impact on total costs (e.g. labour, expensive drugs), for services where there is wide variation in costs between patients, and for centres which are integrated within a larger hospital compared to independent centres (298-301).

Trastuzumab IV was first launched in Ireland in December 2000 while trastuzumab SC was launched in December 2013 (302). The release of trastuzumab SC came at an interesting time when Ireland began to restructure its healthcare funding system from one where hospitals are funded based on historical levels of funding adjusted for activity and patient mix, to a prospective case based payment system known as '*Activity Based Funding*' (ABF) (303). This change is currently being implemented for

inpatient and day-case activity and will subsequently include outpatient services (303). Within the ABF system, previously referred to as '*Money Follows the Patient*', prices will be set initially with reference to average prices, but with an overall aim to implementing best practice prices on an incremental basis (303). Under Ireland's Sláintecare reform policy, work is currently being undertaken to develop the '*Hospital ABF Implementation Plan 2019-2022*' to embed and extend ABF benefits (22).

Acknowledging the contemporaneous reforms in the Irish healthcare sector, the aim of this study was to estimate the total cost of providing trastuzumab treatments to HER2-positive breast cancer patients in two large acute Irish University teaching hospitals within the south/south west hospital group in the year 2018. The perspective of the Irish healthcare service provider was adopted, using a micro-costing approach, and the loss of productivity was calculated from a societal perspective. This is the first economic evaluation examining the impact of switching trastuzumab formulations in the Irish healthcare setting.

5.5 Methods

5.5.1 Hospital 1 – Nurse-led clinic

Hospital 1, a 431 inpatient and 85 day procedure beds teaching hospital, provides general medical, surgical and maternity care to approximately 0.5 million patients of southeast Ireland. This hospital is the designated cancer centre for southeast Ireland. In 2011, a group of patients in this hospital entered into the SafeHer trial (296). In early 2014, this hospital began to switch patients from trastuzumab IV to

trastuzumab SC and decided to introduce a dedicated trastuzumab SC clinic for patients with HER2-positive breast cancer. The adopted approach of moving this cohort of patients out of the day oncology ward was done as an attempt to improve the patient journey. The nursing department, upon consultation with a consultant oncologist, took the decision to resource the trastuzumab SC clinic with a dedicated clinical nurse specialist (CNS), rather than share the resources with the oncology day ward. Clinic times run from 09:30-16:00 where each patient receives an allocated 45-minute treatment slot with a 1:1 patient to nurse ratio.

5.5.2 Hospital 2 – Infusion clinic

Hospital 2 is a teaching hospital in the south of Ireland that has a designated bed complement of 192 beds and caters for up to 38,400 admissions and 72,500 outpatient attendances each year. In late 2015, the pharmacy department in this hospital, upon consultation with a consultant oncologist, made the decision to switch patients from trastuzumab IV to trastuzumab SC. Patients are given either a morning or afternoon appointment in the infusion clinic at this hospital where they are attended to on a first come, first served basis by a CNS as per entry into the patient log.

5.5.3 Cost minimisation analysis

A prospective observational study in a subgroup of HCPs and patients with HER2-positive breast cancer that attended both University hospitals between May and June 2018 was conducted. All data were collected when both hospitals were each visited on four occasions between April and June 2018. Each observation consisted of measuring the time required to perform a specific task related to the preparation and

administration of trastuzumab. To quantify active HCP time, the time actively invested in carrying out the tasks where differences between the routes of administration had been predicted, was observed. **Figure 5.1** shows the tasks that both trastuzumab SC and IV treatment pathways have in common and where the related time estimates were recorded. Patients receiving adjuvant pertuzumab treatment were excluded. All observations were made using a stopwatch. Patient treatment room times (time between entrance and exit from treatment room), were inferred from active HCP times. Although not enough sample time estimates were recorded for each task to resemble a time and motion study, the estimates gathered were verified by the HCPs involved in the study as being a true reflection of average times spent on tasks in routine clinical practice. An average time for each task was subsequently calculated and used in the cost analysis. This methodology has been previously observed in the literature (246, 304). When a sufficient amount of time estimates was recorded for a particular HCP activity associated with trastuzumab preparation, compounding and administration, Student's *t* test was performed for the two groups. In all these instances, results were statistically significant (*P* values < 0.05). Overall, a micro-costing approach was adopted.

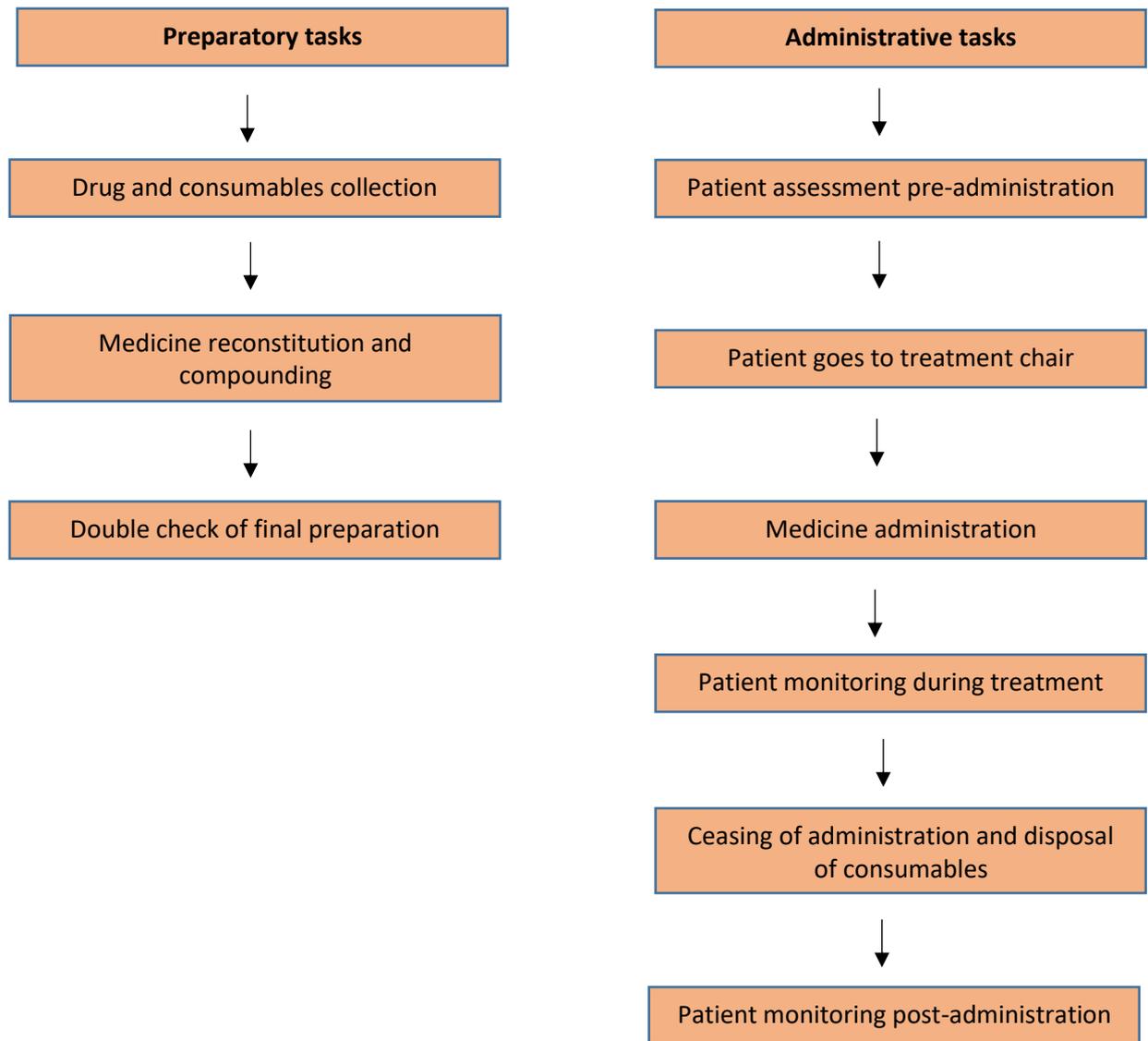


Figure 5.1 Common tasks conducted in the preparation and treatment of trastuzumab SC and IV

Direct and indirect costs were calculated. Direct costs included HCP costs for the tasks observed (nurses, pharmacists, and pharmacy technicians), costs of consumables, and drug costs. Indirect costs included the cost of lost productivity. Although both hospitals had been using trastuzumab SC since 2015, contemporaneously available healthcare costs, expressed in Euros (€) using 2018 prices (unless otherwise stated), were chosen. These updated costs provide a more accurate representation of current

spending in the healthcare sector and are more useful in the preparation of a budget impact analysis, if required (305). The perspective of the Irish public healthcare provider, the HSE, and a societal perspective were adopted. Evidence on resource use and patient health outcomes were collected by the research team during the course of the study and a retrospective review of patient medical records was conducted. However, this was of no major concern in this study given that both trastuzumab formulations are clinically equivalent (295). The time horizon for the study was less than 2 months thus discounting was not required. Multiple cost components were included in the analysis and are described. The mid-point of the HSE healthcare professional pay scale was used and adjusted according to guidelines for conducting economic evaluation in Ireland (60, 306). Salary was adjusted for employers' insurance cost, pension payments and general overheads (see **Table 5.1**). While the switching process in hospital 1 began in 2014 and in hospital 2 in 2015, the 2018 unit cost estimates were deemed appropriate for the analysis as medical inflation in Ireland was relatively stable during this period.

Table 5.1 Costs of healthcare workers

Job description	Gross annual salary (€)^(a)	Total cost (€)/year^(b)	Total cost (€)/min
Pharmacist	48,071	67,179	0.60
Pharmacy technician	38,447	53,730	0.48
Clinical nurse specialist	52,393	73,219	0.65
Staff nurse	37,508	52,417	0.47
<p>(a) April 2018 Revised HSE Consolidated Pay scales (306). (b) The mid-point of the HSE pay scale was used and adjusted according to guidelines for conducting economic evaluation in Ireland (60, 306).</p>			

The costs of consumables were determined by retrieving invoices issued from the finance department from one of the large acute Irish University teaching hospitals in 2018 and calculating unit costs (307) (see **Table 5.2**). Drug costs were calculated according to the 2017 reported ex-factory prices (exclusive of value added tax (VAT)) of trastuzumab IV 150 mg (€567.69) and trastuzumab SC 600 mg (€1,645.24) (308). The medicinal brand of trastuzumab used in both hospitals was Herceptin® and patients were administered the trastuzumab SC formulation via a SID (294). All calculations were performed taking an average patient weight of 72.05 kg (average weight in Irish women aged 36–64 years (309)) treated with trastuzumab for 17 triweekly dosing cycles according to the data sheet guidelines where 17 cycles is considered one year of treatment i.e. a full treatment cycle. Patient weights were retrieved from CliniChemo pharmacy management software. Patients' date of births and sex were retrieved from i.PM (i.Patient Manager). In line with the standard clinical practice, all vials were considered used (vial sharing) in patients treated with trastuzumab IV resulting in no drug wastage. The effect of possible differences between reported and financed prices was assessed in a sensitivity analysis where discounts of 15% in the ex-factory price of the vial of trastuzumab IV and between 15 and 20% in the ex-factory price of trastuzumab SC were applied. These rates are believed to mimic national current commercially sensitive transactions offered by pharmaceutical manufacturers on biological medicines to Irish hospitals and are corroborated by the literature (310, 311). The effect of differences in the weight of patients was analysed in another sensitivity analysis in which the costs of treatment in patients weighing between 65 and 75 kg were calculated. Vial sharing (no drug wastage) and dose banding tables from the NCCP (312) were used in association with

the recommended triweekly maintenance dose of 6 mg/kg of body weight for trastuzumab IV (294).

Indirect costs were estimated using the human capital method (313) for inferred patient treatment room time. As applied in healthcare evaluation, the human capital approach has largely been used to value changes in the amount of time individuals are able to allocate to paid work as a result of illness or programmes to alleviate ill-health (314). According to this approach, the gross wage becomes the unit of value for changes in paid working time resulting from healthcare programmes (314). In the context of this study, where the healthcare programme (trastuzumab treatment) aims to reduce the patient's overall mortality risk, the change in productivity cost is represented by the present value of the stream of additional days in paid work over the duration of the patient's treatment cycle, where each day is valued using the gross wage. The average income liable for social insurance in Irish women aged 15-84 according to the Irish Department of Social Protection and Revenue Commissioners data, adjusted according to current (2018) consumer price index inflation, (€27,206.40) (315, 316) was used in conjunction with the average recorded unemployment rate for Irish women aged 25–74 as of 2017 (5.4%) (317), and the average hours worked by women per week in paid employment in 2016 (31.7 hours) (318).

5.5.4 Guidelines and ethical considerations

This analysis followed the CHEERS guidelines for reporting health economic evaluations (259) (see **Appendix XIV**). Ethical approval for this study was obtained

from the clinical research ethics committee (institutional review board) of the local teaching hospitals network (see **Appendix XV**).

5.6 Results

5.6.1 Direct costs

5.6.1.1 Cost of consumables

The cost of consumables per treatment cycle was €56.28 for trastuzumab IV and €25.91 for trastuzumab SC, a difference of €30.37 excluding the drug costs. For a complete 17-cycle treatment, the cost would be €956.76 for trastuzumab IV and €440.47 for trastuzumab SC, resulting in a saving of €516.29 per patient (see **Table 5.2**).

Table 5.2 Costs of consumables in patients treated with trastuzumab IV or trastuzumab SC during a treatment cycle

Different stages of a complete treatment cycle	Cost of preparing 441mg dose (3x150mg vials) of trastuzumab IV (€) (72.05kg patient ^{(a),(b),(c)})		Cost of preparing a 600mg dose of trastuzumab SC ^(c) (€)	
	Number of items	Cost ex-VAT	Number of items	Cost ex-VAT
Equipment needed				
Pre-cleaning of LAF				
70/30 IPA wipes	8	7.04	0	0
Preparation				
70% alcoholic wipes	20	1.40	14	0.98
70/30 IPA wipes	8	7.04	8	7.04
Sharps bin	1	1.35	1	1.35
Sterile surface mats	2	2.80	2	2.80
Chemo protect gowns	1	4.67	1	4.67
Face masks	1	0.68	1	0.68
Hand gloves	0	0	2	0.04
Elbow length sterile gloves	1	2.10	0	0

Different stages of a complete treatment cycle	Cost of preparing 441mg dose (3x150mg vials) of trastuzumab IV (€) (72.05kg patient ^{(a),(b),(c)})		Cost of preparing a 600mg dose of trastuzumab SC ^(c) (€)	
Equipment needed	Number of items	Cost ex-VAT	Number of items	Cost ex-VAT
Head cap	1	0.02	1	0.02
Mini grip bags	1	0.08	1	0.08
Compounding				
Trastuzumab 150mg vials ^(b)	3	1669.01	0	0
Water for injection 10ml cartridges	3	0.27	0	0
10ml syringe	1	0.12	0	0
Pink needle	2	0.04	0	0
Seal for infusion bag	1	0.05	0	0
Sodium chloride 0.9% 250ml bag	1	0.79	0	0
30ml syringes	1	0.30	0	0
70/30 Sterile wipes	4	0.28	1	0.07
Clinichemo labels	2	0.04	2	0.04
Flag label	0	0	1	0.04
Green poly bags	1	0.06	1	0.06
Trastuzumab 600mg vial	0	0	1	1,645.24
5ml Syringe compatible with the closed system device	0	0	1	1.24
Vented vial access device/adapter 20mm	0	0	1	1.74
Cost of running LAF ^(d)	1	0.05	0	0
Administration				
Orange needle	0	0	1	0.02
Sodium chloride 10ml	0	0	1	0.07
Sterile swabs	0	0	1	0.06
Hand gloves	2	0.04	2	0.04
Fabric plasters	1	0.03	1	0.03
Alcoholic 2% chlorhexidine wipes	1	0.02	0	0
Rubber arm band	1	0.45	0	0
Cannula	1	0.70	0	0
Rubber bung for cannula	1	0.84	0	0
Securing tape	1	0.33	0	0
Opaque infusion giving set	1	5.83	0	0

Different stages of a complete treatment cycle	Cost of preparing 441mg dose (3x150mg vials) of trastuzumab IV (€) (72.05kg patient ^{(a),(b),(c)})		Cost of preparing a 600mg dose of trastuzumab SC ^(c) (€)	
Equipment needed	Number of items	Cost ex-VAT	Number of items	Cost ex-VAT
Sodium chloride 50ml	2	1.30	0	0
Post-cleaning of LAF				
70/30 IPA wipes	8	7.04	0	0
Total Cost (ex-VAT):		1714.77		1,666.31
VAT on injectables and all consumables 23% VAT rate (319, 320):		394.40		383.25
Total Cost (incl. VAT):		2109.17		2049.56
Key: IV: Intravenous; SC: Subcutaneous; VAT: Value Added Tax; LAF: Laminar air flow unit; IPA: Isopropyl alcohol				
<p>(a) The National Adult Nutrition Survey, which provides average weights, was used in the cost of compounding trastuzumab IV (Women: age 36-50 years = 70.5kg, age 51-64 years = 73.6kg, thus the mean weight for these prevalent age categories found with HER2-positive breast cancer is 72.05kg) (309).</p> <p>(b) Dose banding information on trastuzumab IV provided by the NCCP for a 72.05kg patient required 441mg of drug (assume vial sharing/no drug wastage) at a maintenance dose of 6mg/kg (312) (initial loading dose was excluded). A 450mg dose is prepared in clinical practice to attain 441mg of drug.</p> <p>(c) Cost of consumables were retrieved from invoices provided by the finance and resource department of the hospital 2 (307).</p> <p>(d) Average cost of using a LAF for 900 seconds as per HCP trastuzumab reconstitution time where a conversion rate of 1 United States Dollar equals 0.86 Euros as of June 2018 was applied (321). Trastuzumab IV was compounded by aseptic technique in the LAF. Trastuzumab SC was reconstituted safely on the bench using the closed system for immediate administration.</p>				

5.6.1.2 Healthcare professional costs

On average, the cost of HCP time invested in the preparation and administration of trastuzumab was €44.93 per cycle of trastuzumab IV and €9.83 per cycle of trastuzumab SC (see **Table 5.3** and **Table 5.4**). For a complete 17-cycle treatment, this would result in a cost of €763.81 for trastuzumab IV and €167.11 for trastuzumab SC, with a cost differential of €596.70. Extrapolating these results to a hospital treating

25 patients per year with trastuzumab, as per hospitals in this study, the total HCP cost would be €19,095.25 if all patients received trastuzumab IV and €4,177.75 if all patients received trastuzumab SC, with an average saving of €14,917.50 (-78%) favourable to trastuzumab SC.

Table 5.3 Cost description associated with trastuzumab subcutaneous preparation, compounding and administration

Healthcare professional activity	Recorded time estimate in Hospital 1 (secs)	Unit cost (€)	Recorded time estimate in Hospital 2 (secs)	Unit cost (€)
Pre-check of prescription by pharmacist	55	0.55	53	0.53
Medicine preparation by pharmacy technician			54	0.43
Pharmacist double check of medicine			10	0.10
ID, blood pressure, temperature, pulse, blood tests, weight and ECHO check by CNS	342	3.71	331	3.59
Staff nurse double check of medicine	55	0.43		
Tray preparation for drug administration by CNS	15	0.16	10	0.11
CNS preparation (gloves and gowning)	108	1.17	113	1.22
Patient preparation (legs swabbed with alcohol wipe) by CNS	15	0.16	12	0.13
Medicine preparation by CNS	45	0.49		
Injection administration time by CNS	310	3.36	280	3.03

Healthcare professional activity	Recorded time estimate in Hospital 1 (secs)	Unit cost (€)	Recorded time estimate in Hospital 2 (secs)	Unit cost (€)
Patient after care (wipe and plaster) by CNS	20	0.22	25	0.27
Total	965 (16.08 minutes)	10.25	888 (14.80 minutes)	9.41
Average HCP time of both hospitals	15.44 minutes		Average HCP cost of both hospitals	€9.83
Key: CNS: Clinical nurse specialist; ID: Identification; ECHO: Echocardiogram; HCP: Healthcare professional				

Table 5.4 Cost description associated with trastuzumab intravenous preparation, compounding and administration

Healthcare professional activity	Recorded time estimate in Hospital 1 (secs)	Unit cost (€)	Recorded time estimate in Hospital 2 (secs)	Unit cost (€)
Pre-check of prescription by pharmacist	119	1.19		
Pre-check of prescription and tray materials by pharmacist			307	3.07
Preparation of medicine tray and alcohol wipe down of items by pharmacy technician	243	1.94	122	0.98
Compounding of medicine by pharmacy technician in LAF	998	7.98	882	7.06
Pharmacist double check of medicine	150	1.50	33	0.33
ID, blood pressure, temperature, pulse, blood tests, weight and ECHO check by CNS	351	3.80	372	4.03
Staff nurse double check of medicine	54	0.42	49	0.38

Healthcare professional activity	Recorded time estimate in Hospital 1 (secs)	Unit cost (€)	Recorded time estimate in Hospital 2 (secs)	Unit cost (€)
Tray preparation for drug administration by CNS	182	1.97	200	2.17
CNS preparation (gloves and gowning)	102	1.11	99	1.07
Patient preparation (cannulation) by CNS	401	4.34	345	3.74
Injection administration by CNS	1800	19.50	1800	19.50
Patient after care (wipe and plaster) by CNS	182	1.97	167	1.81
Total	4,582 (76.37 minutes)	45.72	4,376 (72.93 minutes)	44.14
Average HCP time of both hospitals	74.65 minutes		Average HCP cost of both hospitals	€44.93
Key: CNS: Clinical nurse specialist; LAF: Laminar air flow unit; ID: Identification; ECHO: Echocardiogram; HCP: Healthcare professional				

5.6.1.3 Drug costs

In the base case (reported ex-factory price inclusive of a VAT rate of 23% (319)) and a national average patient weight of 72.05 kg (309)), the total cost of a 17-cycle treatment would be €34,898.97 for trastuzumab IV and €34,401.97 for trastuzumab SC, resulting in a difference of €497.00. In the first sensitivity analysis (discount of 15% for trastuzumab IV and a range of discounts from 15% to 20% for trastuzumab SC), the cost differences between treatments ranged from €1,027.84 to €2,747.93 in favour of trastuzumab SC. In the subsequent sensitivity analysis (considering patient weights between 65 and 75 kg and where banded doses for trastuzumab IV recommended by the NCCP, were applied (312)), the cost differences between

treatments ranged from €-2,826.71 to €497.00. More extreme weights (i.e. patients ≥80 kg) could reach savings greater than €3,820.71.

5.6.2 Indirect costs

The average patient treatment room time for both study sites was 841 seconds for trastuzumab SC and 3,052 seconds for trastuzumab IV (assuming no waiting times for patients). Estimated indirect costs according to lost productivity inferred by patient treatment room time for a 17-cycle treatment per patient were €243.74 (loss of 2.15 working days) for trastuzumab IV and €67.15 (loss of 0.60 working days) for trastuzumab SC. Trastuzumab SC resulted in lower indirect costs per patient compared with trastuzumab IV.

5.6.3 Total costs

Direct costs were €36,619.54 for trastuzumab IV and €35,009.55 for trastuzumab SC, a net difference of €1,609.99 in favour of trastuzumab SC. When indirect costs were added, replacement of trastuzumab IV by trastuzumab SC for a full 17-cycle treatment would save €1,786.58 (see **Table 5.5**).

Table 5.5 Total costs in patients treated with trastuzumab IV or trastuzumab SC

Costs	IV (€)	SC (€)	Difference (€)
Direct costs	36,619.54	35,009.55	1,609.99
Healthcare professional costs	763.81	167.11	596.70
Consumable costs	956.76	440.47	516.29
Drug costs	34,898.97	34,401.97	497.00
Indirect costs	243.74	67.15	176.59
Total costs	36,863.28	35,076.70	1,786.58

5.7 Discussion

This study describes active HCP time invested in the preparation and administration of trastuzumab. A time saving of 79% was accrued by the replacement of trastuzumab IV with trastuzumab SC. In fact, the authors believe this is the highest recorded active HCP time saving where other studies report time savings of 51% in Spain, 48% in Canada and Russia, 36% in France, 31% in Denmark and 15% in Switzerland (322). Greater available HCP time could result in improvements in the quality of care, with more time free for monitoring, for other relevant medical duties, or indeed for providing patient information or comforting. In addition, by utilising trastuzumab SC in the place of trastuzumab IV, a saving of €596.70 per patient in active HCP time for a full 17-cycle treatment was gained. This result is consistent with those of international studies (323-326).

The reduction in patient treatment room time resulted in a difference in indirect costs of €176.59 per 17-cycle treatment in favour of trastuzumab SC, a conservative estimate that only considered lost productivity between entering and leaving the patient treatment room. Moreover, this reduction in patient treatment room time could allow for the treatment of the same number of patients with fewer resources or more patients with the same level of resources. As well as the economic implications, quality of life may improve with the time savings associated with trastuzumab SC. Indeed, a key finding of the PrefHer study was that patients favoured trastuzumab SC as it accumulated more time saved for them relative to trastuzumab IV treatment (297). Hence, more than just an estimate of costs from the social perspective, according to preferences conveyed, we see that the patient can be the

main beneficiary. Quality of life is especially important to those patients with metastatic breast cancer as theirs is a chronic illness and so minimising the time spent in the hospital setting is an important factor in survivorship.

Drug cost savings from switching to trastuzumab SC may be underestimated in this study. The National Adult Nutrition Survey was used in calculating the cost of compounding trastuzumab IV (Women: age 36-50 years = 70.5kg, age 51-64 years = 73.6kg) where the mean weight for these prevalent age categories found with HER2-positive breast cancer is 72.05kg. This average weight was an underestimate of the true patient weight as Ireland tackles a rising obesity problem (327). In this study, the mean patient weight between both centres was 73.44 kg with a range between 43.5kg-125kg. Therefore, by using the average recommended weight of 72.05kg, the trastuzumab IV formulation may appear less costly than it actually is in practice. As per sensitivity analyses, drug costs for trastuzumab IV were currently lower than drug costs for trastuzumab SC only for patients weighing ≤ 69 kg. For patients weighing ≥ 70 kg, drug costs for trastuzumab IV began to drastically increase relative to drug costs for trastuzumab SC.

In addition, with respect to the recommended weight of 72.05kg, a maintenance trastuzumab IV dose of 6mg/kg (294) would require 432.3mg of drug. This is rounded to 441mg according to the national dose banding tables (312) provided by the NCCP. This results in 9mg of drug remaining after each trastuzumab 150mg vial reconstitution. Over 17 triweekly cycles, this equates to 153mg of drug remaining. In this study, we assume vial sharing and no drug wastage. However, in clinical practice, it is unlikely this amount of drug would be utilised, as 9mg of drug is a very small

quantity to share at each treatment cycle juncture, and vial sharing opportunities do not always arise upon reconstitution. Therefore, it is possible that the cost of 17 triweekly cycles of the trastuzumab IV is appearing €712.22 cheaper per patient than it actually is. A loading dose of 8mg/kg is required for patients when starting trastuzumab IV therapy, and again if patients miss their scheduled dose of trastuzumab IV by more than one week (294). This presents an additional cost for trastuzumab IV which was omitted in this analysis. There is no initial loading dose for starting treatment or missed treatment with trastuzumab SC (328) resulting in this formulation being a more cost-effective option under these circumstances.

Subcutaneous formats of different oncologic therapies have been available since mid-2014, however it is only recently that patient-relevant and hospital benefits are being assessed (322, 329). Although open to debate, the literature appears to favour subcutaneous oncology treatments over intravenous oncology treatments in terms of patient preference, time and cost savings (297, 310, 322, 329-332). A recent ISPOR Special Task Force report identified and defined a series of elements that warrant consideration in value assessments of medical technologies (333). In the report, Lakdawalla *et al.* discuss that some medical technologies offer advantages over existing choices such as simpler dosing schedules, alternative routes of administration, or combination treatments. To the extent such factors improve patient adherence to treatments and health outcomes, they may impact the estimation of the value of the medical technology in the aggregate (334). It is evident from this study that the trastuzumab SC formulation offered these advantages when compared to the trastuzumab IV formulation. Trastuzumab SC also reduces the need

for cannulation of patients whose veins are often compromised due to previous therapies and tests.

5.7.1 Limitations

The main limitation of the study was that not enough time estimates were recorded to conduct a time and motion analysis. Although the estimates gathered were verified by the involved HCPs as being a true reflection of average times spent on tasks in routine clinical practice, a time and motion study, which gathers data on HCP time required to complete the observed tasks, would reduce uncertainty surrounding such inputs. As per other time and motion studies investigating this trastuzumab formulation switch, it would have been desirable to record hospital time (time between entry and exit from the hospital), and patient travel to the hospital, or the time lost by accompanying persons, by means of patient interview when calculating indirect costs (310). These measurements would capture a broader societal perspective. Two recent time and motion studies have demonstrated that a transition to both trastuzumab and rituximab SC formulations from their respective IV formulations resulted in patient chair and active HCP time savings (322, 330).

This study was carried out in only two centres where differences in clinical practice exist. At times, it was difficult to compare clinical practice procedures for the analysis. However, as this study was conducted in routine clinical practice settings yielding real world data, as opposed to a study within/alongside a RCT, the results are more generalisable. This study's design and setting may also explain why the active HCP time savings value of 79% was numerically higher than those corresponding values reported by time and motion studies conducted within open-label randomised

crossover studies (322). Nonetheless, as trastuzumab SC gains traction in the Irish healthcare setting; further research in more hospital sites should be conducted to corroborate these study findings.

At the time of data collection, one of the 48 patients receiving trastuzumab treatment was male. However, as the epidemiology of HER-2 positive breast cancer is much greater in females than males (335), indirect costs and loss of productivity were calculated using statistics based on data gathered for Irish women. If this method was calculated for males, it is likely the indirect costs and loss of productivity would be greater based on data gathered for Irish men (315).

A potential limitation in this study was the issue of '*dead time*' i.e. the five minute time period required for trastuzumab IV to dissolve upon reconstitution (294) and its 30 minute infusion period. While it was potentially possible that the HCP could conduct other medical duties during this dead time, such tasks were impossible to cost. The issue of dead time and potential medical opportunity cost is a controversial one in the field of costing (336). In addition, as best clinical practices are adopted in these two large Irish University teaching hospitals (e.g. vial sharing etc.); it was observed that the CNS upheld their duty of care by monitoring patients closely during the 30-minute trastuzumab IV infusion period for fear of ADR occurrence. This limited the ability of the CNS to perform other activities in parallel.

Regarding trastuzumab IV treatment, patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms (294). For trastuzumab SC, patients should be observed for six hours after

the first injection and for two hours after subsequent injections for signs or symptoms of administration-related reactions (328). Follow-up time was excluded from the cost minimisation analysis as no cost differential existed. In clinical practice, patients were strongly advised to remain in the clinic for the recommended follow-up time, but this was seldom adhered to by patients. The resulting variability in follow-up time from patients was not measured which means the loss of productivity may be underestimated in this study. Paracetamol treatment (by mouth or by IV infusion) was recommended for patients receiving both trastuzumab IV and SC treatment. Therefore, as no cost differential existed, it too was excluded from the cost analysis. In reality, some patients would take paracetamol while others would refuse.

5.7.2 From evidence to policy

At present, it can be argued that this study is only of interest to hospital budget decision-makers within the south/south west hospital group in Ireland. A similar issue arose in a study where the results of an economic evaluation of propofol/fentanyl compared with midazolam/fentanyl on recovery in the intensive care unit following cardiac surgery was only of interest to the local hospital (337). However, more Irish hospitals are beginning to use trastuzumab SC, and following its successful implementation in Europe, Oceania and South America (310, 331, 338), it is envisaged that this formulation will penetrate the North American oncology landscape next. Furthermore, in relation to the current oncology field, biosimilar trastuzumab IV is now available (339). It has been approved in Ireland since June 2018, where the biosimilar trastuzumab IV 150mg vial Herzuma[®] yields a drug cost of €401.86 (exclusive of VAT) (340). This is in comparison to the Herceptin[®] IV 150 mg vial which

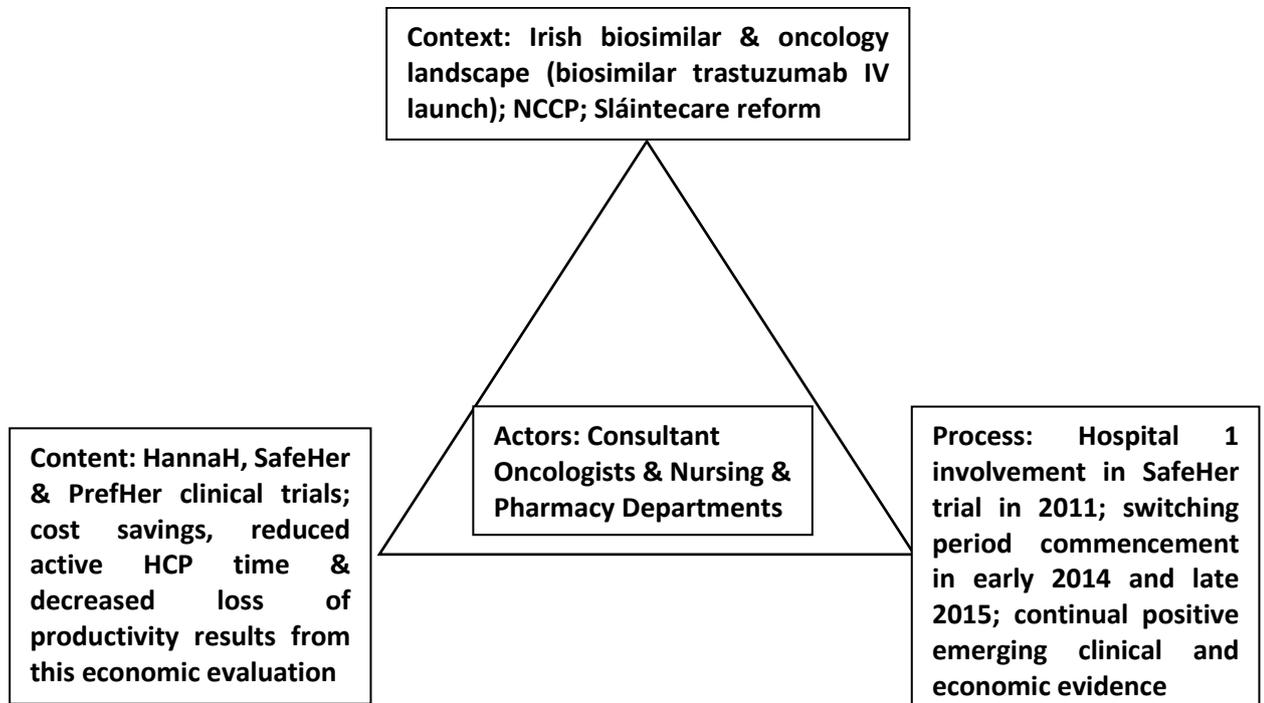
yields a drug cost of €567.69 (exclusive of VAT) (308). The individual summary of product characteristics documents for both medicinal products appear almost identical (294, 339), thus it can be assumed that medicine reconstitution and administration tasks are equivalent. This means the only major differential between the two products is drug acquisition cost. It is also worth noting that local commercially sensitive price reductions are sometimes offered to payers who switch to biosimilar medicines (341). It will be interesting to see what impact biosimilar trastuzumab will have on the Irish and international markets and indeed how it will affect trastuzumab SC market penetration.

In this study, an attempt to capture the societal perspective was undertaken by calculating the loss of productivity via the human capital method as well as presenting the more commonly reported healthcare payer perspective. Sanders *et al.* recommended for the sake of consistency and comparability, analysts should report 'reference cases' from two perspectives—the healthcare sector perspective and the societal perspective (58). This was also corroborated by an ISPOR Special Task Force report (59). In addition, Olsen and Richardson argue that part of productivity effects may be included to the extent that it results in increased resources available for healthcare (342). In fact, if the trastuzumab SC formulation was taken out of the secondary care setting and supplied to patients via their local pharmacy for self-injection at home, the loss of productivity element would virtually be eliminated as patients could avoid going to hospital. In conjunction, this would alleviate some of the workload that the exhausted secondary care system already encounters. Ireland has devised a ten-year plan for health reform through political consensus called Sláintecare which is currently underway (23). Its aim is to establish a universal, single-

tier health service where patients are treated solely on the basis of health need. However, it also plans to re-orient the health system '*towards integrated primary and community care that is consistent with the highest quality of patient safety in as short a time-frame as possible*' (21). In line with the overarching aim of Sláintecare, the transplantation of trastuzumab SC treatment to the primary care sector would also satisfy patient needs who prefer home and community-based medical treatments (343).

This is the first study to evaluate the economic, financial and clinical impact of switching patients from trastuzumab IV to trastuzumab SC in Ireland where recommendations from the CHEERS statement were implemented to ensure that this analysis presents a transparent high-quality evaluation. Accurate cost data are essential for ensuring breast cancer services are effective, efficient, and equitable, and such costing information should be used to guide policy, planning and implementation in this field. This is particularly relevant as the Irish healthcare funding system is currently undergoing restructuring (22, 303). As demands on breast cancer services increase due to greater numbers of presenting patients (344) with more complex care needs, the cost data presented in the analysis will be available for cost-effectiveness evaluations of new drugs, technologies, and proposed models of care under Sláintecare reform (22, 23). The cost data are of particular interest to the NCCP who manages, organises and delivers cancer services on a whole population basis in Ireland (345). The policy decision to switch patients to trastuzumab SC at a regional level has proven successful to the extent that upon advice from the NCCP, other Irish hospitals began to follow by example. **Figure 5.2** briefly summarises the

content, context and process underpinning the policy decision using the HPT framework (46).



Key: HCP: Healthcare Professional; IV: Intravenous; NCCP: National Cancer Control Programme

Figure 5.2 Walt and Gilson policy triangle model describing trastuzumab formulation switching policy

5.8 Conclusion

As portrayed by the HPT framework, the interrelated factors which led to the replacement of trastuzumab IV by trastuzumab SC within two large acute Irish teaching hospitals has proven to be a more cost-effective approach reducing active HCP time, patient treatment room time, and thus improving patients' quality of life. With respect to the Irish healthcare landscape, these reductions in time result in economic savings, more efficient resource use, and improved quality of care. Trastuzumab SC reduces the cost of consumables. Dependent on the patient's weight

and the hospital's policy on vial sharing, trastuzumab SC did not always result in drug cost savings. A full treatment cycle of trastuzumab SC resulted in total estimated direct cost savings of €1,609.99. Every year, between 400 and 500 new cases of HER2-positive breast cancer present in Ireland (344) where such patients would be potentially eligible for treatment with trastuzumab. The widespread use of trastuzumab SC for these patients would not only result in direct cost savings but would also lead to a reduction in indirect costs due to a decrease in the loss of productivity. These clinical and economic aspects demonstrate that trastuzumab SC results in benefits for patients, HCPs, and indeed, wider society.

6 Chapter 6 Out of pocket or out of control: a qualitative analysis of healthcare professional stakeholder involvement in pharmaceutical policy change at national level

6.1 Chapter description

In this chapter, a public health-related pharmaceutical policy that has affected all publicly insured citizens in Ireland since its introduction approximately one decade ago was investigated. Evidence was gathered by conducting semi-structured interviews with relevant stakeholders to inform future policy process development. The pharmaceutical policy concerns the mandatory co-payment fees attached to prescription medicines on the Irish public health insurance scheme. It is unknown what impact these changes have on relevant stakeholders who work at the coalface of this labile policy. A qualitative study using purposive sampling alongside snowballing recruitment was used to generate compelling evidence. The HPT framework was used to depict the interrelated factors which underpin this national pharmaceutical policy. The other authors of this chapter and publication reviewed the chapter and gave their input and advice during the study. On June 11th, 2020, the following published paper was submitted to the Department of Health, the Irish College of General Practitioners, the Irish Medical Organisation, the Irish Pharmacy Union, and the Pharmaceutical Society of Ireland to inform future policymaking on this topic.

6.2 Publication

The work of this chapter has been modified and published as O'Brien GL, Sinnott SJ, O'Flynn B, Walshe V, Mulcahy M, Byrne S, Out of Pocket or Out of Control: A Qualitative Analysis of Healthcare Professional Stakeholder Involvement in Pharmaceutical Policy Change in Ireland, *Health Policy*, 2020, 124(4):411-418, DOI:10.1016/j.healthpol.2020.02.011 (see Appendix XVI for full text).

6.3 Abstract

6.3.1 Background

Mandatory co-payments attached to prescription medicines on the Irish public health insurance [General Medical Services (GMS)] scheme have undergone multiple iterations since their introduction in October 2010. To date, whilst patients' opinions on said co-payments have been evaluated, the perspectives of community pharmacists and general practitioners (GPs) have not.

6.3.2 Objective

To explore the involvement and perceptions of community pharmacists and GPs on this pharmaceutical policy change.

6.3.3 Methods

A qualitative study using purposive sampling alongside snowballing recruitment was used. Nineteen interviews were conducted in a southern region of Ireland. Data were analysed using the Framework Approach.

6.3.4 Results

Three major themes emerged: 1) the withered tax-collecting pharmacist; 2) concerns and prescribing patterns of physicians; and 3) the co-payment system – impact and sustainability. Both community pharmacists and GPs accepted the theoretical concept of a co-payment attached to the GMS scheme as it prevents moral hazard. However, there were multiple references to the burden that the current method of co-payment collection places on community pharmacists in terms of direct financial

loss and reductions in workplace productivity. GPs independently suggested that a co-payment system may inhibit moral hazard by GMS patients in the utilisation of GP services. It was unclear to participants what evidence is guiding the GMS co-payment fee changes.

6.3.5 Conclusion

Interviewees accepted the rationale for the co-payment system, but reform is warranted.

6.4 Introduction

According to the WHO, a co-payment (user charge or user fee) is defined as '*money people are required to pay at the point of using health services covered by a third party such as the Government, a health insurance fund or a private insurance company*' (346). These out-of-pocket fees are paid by the insured patient on many health services such as outpatient visits, dental care, inpatient care and prescription medicines. There are many documented advantages to having a co-payment attached to prescription medicines; cost containment, moral hazard prevention and revenue generation (347). Disadvantages include lower rates of drug treatment, worse adherence among existing users, more frequent discontinuation of therapy, and increased patient financial responsibility (348, 349). Co-payments are a common feature of western health care systems (346).

The GMS scheme in Ireland is a tax-funded, means-tested, public health insurance scheme (3). It provides many health benefits including inpatient and outpatient care, GP services and prescription medicines to those who meet the eligibility criteria (350), all free at the point of access. Currently, 32% (1,565,049) of the Irish population receive healthcare on this scheme (5). Patients who avail of health coverage on the GMS scheme are known as medical card holders. In October 2010, in an attempt to counteract rising Government expenditure amid a severe economic downturn post 2008, and to reduce medicine wastage, the DoH introduced a €0.50 co-payment per prescription item, capped at €10 monthly, for the first time, for publicly insured GMS patients (351). Since then, the GMS prescription medicine co-payment, also known as the GMS levy, has undergone numerous iterations in both monetary value per

prescription medicine and in monthly cap fee (capped after the first 10 prescription medicines per month for each of the GMS co-payment iterations). Indeed, this levy acts like a form of taxation. **Figure 6.1** below reveals a timeline of all recent GMS co-payment changes and includes the introduction of different co-payments for separate age groups which was first introduced in March 2017.

In the Irish context, patients were mostly accepting of the initial €0.50 co-payment with some reservations concerning an increased price and the way in which generated revenue would be used by Government (351). This aligns with international patient perspective where most patients accept paying toward medication in principle (352-354). Contemporary quantitative analysis on the GMS co-payment increases has demonstrated that the €0.50 co-payment was associated with reductions in adherence ranging from -2.1% to -8.3% for essential medicines and reductions in adherence of -2% to -9.5% for less essential medicines (355). The €1.50 co-payment generally resulted in smaller reductions in adherence to essential medicines with anti-depressant medications being the exception with a decrease of -10.0% after the co-payment increase (355). For publicly insured families with children, a detrimental effect on health was not found from small co-payments (€0.50, €1.50 and €2.50) on prescription items (6).

The objective of the study was to retrieve insight into the engagement and opinions of experienced HCPs on the GMS co-payment policy changes. Using the qualitative data collected from interviews, this analysis aims to inform healthcare policymakers on this specific pharmaceutical policy as Ireland is currently in the process of attempting to deliver whole system reform and universal healthcare known as

Sláintecare for all its citizens (23). This study adds to the literature by investigating the stakeholder involvement of HCPs in co-payments attached exclusively to prescription medicines, which to date, has not been researched.

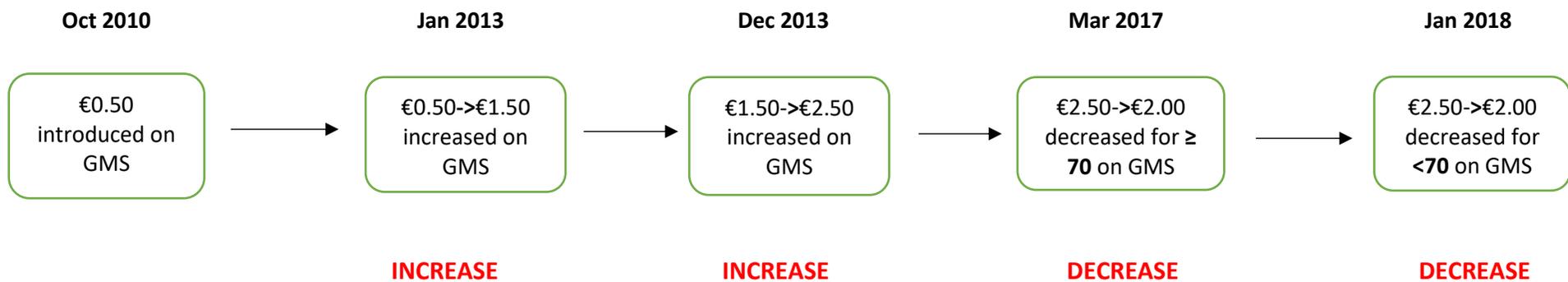


Figure 6.1 Timeline review of recent GMS co-payment introductions and changes 2010-2018

6.5 Methods

6.5.1 Study design, setting and sampling

The sampling frame for this study included registered community pharmacists and GPs who had been consistently practising for at least six months prior to the first GMS co-payment introduction in October 2010 to April 2019 (data collection cessation). Nineteen semi-structured interviews (13 community pharmacists, 6 GPs) were conducted between January 2018 and April 2019 where HCPs working in five different socioeconomic areas were interviewed in the province of Munster, Ireland (see **Table 6.1**). Both community pharmacies and medical surgeries were classified by their respective socioeconomic classes via the Trutz Haase Deprivation Index 2016 by electoral division (356). HCPs from both independent and franchise pharmacies were included. Franchise pharmacies were defined as those that consist of several similar businesses which are corporately owned. All medical surgeries in this study were independently owned. Most interviews were conducted in an urban practice save for two marginally above average medical surgeries and one marginally above average community pharmacy which were considered to be rural practices (357). Varying socioeconomic and workplace structures and locations were included to ensure that a broad range of thoughts and attitudes could be obtained from a range of social circumstances, age, gender, and work place practices. All interviewees declared they had no obvious bias to declare on this topic. This was asked to ensure that selection was not based on prior knowledge of interviewee involvement on this topic.

Interviewing was chosen as the preferred data collection method for many reasons. First, given that some of the interviewees owned their own pharmacy/medical surgery, the topic of work place practices, medicines, and money/financial loss could be considered a sensitive subject. Secondly, focus group dynamics can be unpredictable where more in depth coverage, with a lower risk of social desirability bias, is possible when interviewing an individual (64). Participant information letters (see **Appendix XVII**) and consent forms (see **Appendix XVIII**) were made available. Participants were sampled using purposive and snowball-sampling methods (64, 358). An initial 'core set' of potential participants were identified by the research team through personal contact. These participants were then asked to suggest other individuals they believed could assist with the study. Participants were free to decline the invitation to partake but did this not happen. Once HCPs agreed to be interviewed, the interviewer explained who they were, clarified the aims and objectives of the study, and assured participants of anonymity and data confidentiality. Participants were asked for verbal and written consent. The researchers sought to address reflexivity during all aspects of the study.

Table 6.1 Distribution of practices by location and ownership status

Practice location	Independent	Franchise	Total
Affluent	2	1	3
Marginally above average	7	2	9
Marginally below average	2	0	2
Disadvantaged	2	2	4
Very disadvantaged	1	0	1
Total	14	5	19

6.5.2 Data collection

Two very similar topic guides were developed in order to achieve structured feedback from participants (see **Appendix XIX**). One topic guide was targeted at community pharmacists whilst the other was used when interviewing GPs. Given that both topic guides were designed to have a strong resemblance, data from both community pharmacists and GPs were analysed together as one combined HCP data pool. Both topic guides drew on existing related literature (351, 355, 359-364), and the professional experience of the research team. The topic guides were initially piloted with two pharmacists and one GP and were amended as the interviews progressed to obtain current and topical feedback from participants. The decision was made to exclude the pilot interviews from the analysis. The pharmacist topic guide underwent four iterations whereas the GP topic guide underwent two iterations. Many issues were discussed with both pharmacist and GP participants and some of these are highlighted in **Table 6.2**. All interviews consisted of one interviewer and one

interviewee and were recorded and transcribed verbatim using two methods of audio recording: a Dictaphone (Sony IC Recorder ICD-PX240) and a mobile phone device (Samsung Galaxy S6 SM-G920F). Interviews took place in the workplace office of the HCP being interviewed allowing for a quiet and confidential space. Interviews ranged in time from approximately 7 minutes to 30 minutes. A field diary was brought to each interview to record noteworthy observations.

The study did not have a target sample size; rather it aimed to recruit participants until data saturation of key themes emerged. During data collection, before considering further participation recruitment, preliminary data analysis was conducted to highlight when researchers were approaching data saturation (165). In addition, the Francis *et al.* method was intended to be used as a supplementary means to determine data saturation (365). This method involves identifying an initial analysis sample size and then defining a stopping criterion. The stopping criterion is a defined number of interviews that will take place in which no new themes will emerge. It was agreed that data saturation had been reached after 16 interviews with no new themes emerging in the following three interviews.

Table 6.2 Issues discussed in interviews

Topic	Question
Positive/negative aspects of co-payment?	What are your thoughts on the co-payment attached to prescription medicines?
Influence of co-payments on your practices and procedures?	Has the co-payment influenced your practice or procedures in the work place?
Co-payment retrieval?	How easy or difficult is it to retrieve the co-payment?
Patients' perception of co-payment?	How do you think patients perceive paying the co-payment?
Financial loss?	Have you suffered financial loss from patients not paying?
Medicine utilisation?	Do you think the co-payment has influenced patients' utilisation of medicines?
Impact of co-payments on GPs prescribing habits?	Has the co-payment changed the way you prescribe or influence the amount of prescriptions you issue?
Future status of co-payment/policy suggestions?	What do you think the future holds for the co-payment? Should it be increased/decreased/abolished?

6.5.3 Analysis

The Framework Approach was used to identify themes emerging from the data obtained and was chosen because of its relevance in policy change and detailed format in comparison to regular thematic analysis (64, 366). The framework method contained seven key stages that allowed for the categorisation and organisation of the large amounts of data to help develop underlying themes and emerging phenomena. These seven stages consisted of i) transcription ii) familiarisation with the interview iii) coding iv) developing a working analytical framework v) applying the analytical framework vi) charting data into the framework matrix and vii) data interpretation and mapping (55, 367). The framework constructed throughout this process was continually amended and '*tested for fit*'. Language was seldom altered

in an attempt to retain original meaning and context. The analysis was interpretative recognising the interaction between the researcher and the data.

The data were managed through NVivo12 Plus, QSR International software (368). Data analysis was conducted by GOB, a research pharmacist undertaking a clinical pharmacy PhD. Intercoder reliability was used at early stages of the project to ensure a high rate of intracoder reliability on subsequent transcript data analysis. A sample of four random transcripts were coded and indexed by BOF. At the time of data collection, BOF was an undergraduate pharmacy student. Both GOB and BOF discussed arising differences in this process to ameliorate the accuracy of the thematic framework and the application of the framework to subsequent transcripts. Some disagreements in coding arose. The most common reason for disagreement was the generation of redundant labels/codes that described the same phenomenon e.g., dissatisfaction with Government and anger towards the Irish HSE. Through discussion, these indexing discrepancies were resolved (369). Both GOB and BOF had undertaken qualitative data analysis training courses prior to data collection.

6.5.4 Guidelines and ethical considerations

The Consolidated Criteria for Reporting Qualitative Research (COREQ) statement guided study reporting (370) (see **Appendix XX**). Ethical approval was sought from and granted by the Clinical Research Committee of the Cork Teaching Hospitals prior to study commencement (see **Appendix XXI**).

6.6 Results

Nineteen HCPs were interviewed in total each with varying experience (see **Table 6.3**). The Framework Approach produced three main themes as elaborated on below. In the reported analysis, participant pseudonyms were created to provide information about: practice ownership [Independent (*'Indep'*) or Franchise (*'Fran'*); community pharmacist participant number (*'CP1'*) or general practitioner participant number (*'GP2'*)].

Table 6.3 Characteristics of interviewees

Sex	Male	13
	Female	6
Frequency of age groups (years)	35-39	3
	40-44	6
	45-49	4
	50-54	1
	55-59	2
	60-64	0
	65-69	3
Number of years practising	15-19	9
	20-24	5
	25-29	2
	30-34	0
	34-39	1
	40-44	2
Employment status	Full-time	14
	Part-time	5
Year received professional body number	Pre-1980	3
	1980-1984	1
	1984-1989	0
	1990-1994	3
	1995-1999	8
	2000-2004	4

6.6.1 The withered tax-collecting pharmacist

It was unanimously accepted that although the current co-payment system has advantages pertaining to cost containment and waste reduction, the pharmacist is just one party who suffers from its consequences:

“I didn’t study for five years in order to become an organ of revenue collection for the Government, it is outside the terms and conditions of my role and it’s certainly outside the terms and conditions of my contract with the HSE to raise money for the revenue commissioners” IndepCP11.

Pharmacists can occasionally find themselves in “*dangerous situations*” **FranCP12** upon co-payment retrieval, and in scenarios whereby they must supply the medicine without retrieving the co-payment:

“you’re spending your time trying to look after the best interests of the patient and sometimes the best interests of the patient is I need you to take these medications so I’m going to have to sacrifice. My duty of care to you as a patient trumps my duty of care to the state to collect a tax for them. So therefore the net loser in that transaction is the pharmacist who essentially is now working for free” **IndepCP11.**

Pharmacists also expressed a loss in workplace productivity by collecting the co-payment:

“if it’s simply that they’re paying by credit card it’s taking up a minute, two minutes but you add that 100 times a day, your efficiency is gone down dramatically and that’s time that’s taken from something” **IndepCP05.**

Pharmacists too experience patient disgruntlement at the point of transaction:

“I think there is still a lack of understanding that it’s a Government levy as opposed to a personal, pharmacist into-the-pocket levy. That is something that is still an area of confusion, even now” **IndepCP02.**

There was an emergent consensus that pharmacists should not bear the financial loss if a patient cannot/will not pay. When a pharmacist supplies a medicine to a patient who cannot/will not pay, the primary care reimbursement services (PCRS) still deduct this co-payment tax/levy from the pharmacist. In addition, as there is a maximum

monthly co-payment cap for households, if family members are not recognised as one household unit on the electronic PCRS system, the pharmacists bear the resulting financial deficit. As a result, pharmacists have reported large financial losses:

“Tens of thousands of euro for reasons of non-payment, but also for reasons of families weren’t linked properly on the PCRS database. Those are probably the two most common causes of a deficit in what I should have taken in, what the State deducted from me and what I was able to take in” **IndepCP11.**

Pharmacists note that a proportion of GMS patients acknowledge the value of having the co-payment attached to their medicines:

“..... they think they’re getting good value for money and that it’s a good thing for the country...” **FranCP13.**

However, the risk to patient safety which arises from having a co-payment system was recognised by community pharmacists:

“From the pharmacy perspective it has introduced extra administrative issues, therefore has caused a danger, in my view, to patient safety because if you are having to talk to Mrs. Murphy about a blasted prescription charge, when you really should be concentrating on the prescription and the dose and the interactions and all of this.....” **IndepCP05.**

6.6.2 The co-payment system – impact and sustainability

Before the introduction of the co-payment on the GMS, medication stockpiling and wastage was noted as a prominent feature by both pharmacists and GPs:

*“I did a house call and I asked the lady, ‘Oh, where do you keep your tablets?’ In under the stairs I removed at least 10 Tesco® plastic shopping bags full of unused medication. They were stockpiled in the thing.....There was bags of them.....going back like 10 years.....There was like tens of thousands of tablets that she wasn’t taking” **IndepGP02.***

Medication waste seems to be ongoing but not at the level that it once straddled:

*“unfortunately, we see it particularly again when patients pass away, the big black bag of unused medication, I don’t believe the black bags have got any smaller since the October 2010, ‘til January 2018” **FranCP08.***

The consensus from interviewees is that the co-payment system influences medicine utilisation and adherence rates:

*“The PRN stuff would be the first to go, so if there are items they genuinely don’t need, they would be the ones that would first go” **IndepCP04.***

However, some pharmacists advocate:

“the co-payment certainly has disimproved compliance for certain groups of people. So I think in terms of benefits to how people take their medicine, the people that come back regularly for medication, when there was no 2.50 levy or no 50 cent levy, would generally be compliant. There are people that now choose to come back regularly for certain items and not for others or they will take items, run them up and not take them the next month, so they’ll alternate items, you know. So that certainly isn’t beneficial when a patient has to make a decision as to whether their blood pressure is more important than their

cholesterol. You don't feel your blood pressure being high. You don't feel your cholesterol level being high. They would be always the easier ones to drop"

FranCP13.

This is worrying as it means patients must choose between which essential medications to take; this poses a big threat to patient safety. This feature is also observed amongst patients without medical cards and how much more they pay for medication:

"..... It's the poor private paying patient.....They'll come to you and they'll say, 'Look, ok, that blood pressure tablet' and it might be for example an ACE inhibitor, 'what's the cheapest one I can get of that?'" **IndepGP02.**

Most HCPs agree that the co-payment system is a good tool to deter moral hazard but not to generate revenue:

"If it was 50 cents like it had been initially, then there's an understanding of why it's there. Going to 2.50 in 2013 was the one that impacted most..... So, 2.50 would probably be the straw that breaks the camel's back in terms of the amount that patients are going to pay. Being at the 50 cent charge was the one to leave it at. We understood the policy behind it, you know. Trying to increase it up to generate revenue just doesn't make sense from a health point of view" **FranCP13.**

In fact, HCPs recommend eligible patients with a long-term illness (LTI), as classified by the HSE, to switch to the LTI scheme where there is no co-payment on prescription medicines i.e. GMS co-payment (tax) avoidance:

*“we’ve been migrating them (eligible medical card patients) over to the LTI scheme” **IndepCP02** and “if you go online to the Diabetes Ireland website, they’ll tell you, ‘If you’ve a medical card, make sure you get a long-term illness’. So, they’re actually telling people to avoid the levy” **IndepCP11**.*

However, some participants described the unfairness of this scheme which is not means-tested:

*“Why should a long term illness patient, you can have a retired High Court judge, a retired Taoiseach [Irish Prime Minister] who might have Type 2 diabetes availing of all those levies for their cardiovascular medicines, their statins, their aspirin all free of charge, not even a levy paid and somebody with mental health difficulties who could be in very poor social circumstances, on social welfare, having to pay €2. That is grossly unfair” **IndepCP11**.*

Both pharmacists and GPs want the system to remain in place:

*“if Sinn Féin [A left-leaning Irish political party] get into Government, they might promise to abolish it (the GMS co-payment) as a great stroke to the people, but I firmly believe that the people in the medical card system get an excellent service for nothing and that the co-payment is a very small little contribution to the exchequer and it’s tiny in the overall scheme of things” **IndepGP03**.*

Notwithstanding this perspective, it was interesting to note that some interviewees suggest that the co-payment system *“should be means-tested”* in order to reduce health inequalities **IndepGP05**. As well as GPs who believe that: *“GP unions should be involved in co-payment policy because it does affect the workload” **IndepGP01**,*

pharmacists too want to be heavily involved in the co-payment policy. They have many suggestions for co-payment policy improvement:

“The fee should certainly be decreased down back to 50 cent, but with a greater emphasis then on exemptions so that there could be specific patients who shouldn’t have to pay, a greater cohort of patients that shouldn’t have to pay. So, say for example, if a patient is diagnosed with cancer and is entitled to a medical card, then they should be getting the medical card and have it free of charge” **FranCP13**.

6.6.3 Concerns and prescribing patterns of physicians

GPs report that the co-payment has fine-tuned their prescribing habits:

“has made me a little bit more conscious of what I prescribe for patients in that are they going to take it? Are they going to pay 2.50? Ok, it doesn’t sound like a lot, but do you know, whatever it is, it’s nearly €30 a year, whatever, per item and patients on a social welfare budget, that’s an awful lot of money. So it makes me a little bit more conscious of it” **IndepGP06**.

In addition, the co-payment seems to create additional dialogue in the medical surgery *“Maybe I get into the conversation of what they need this month more so than I would have in the past”* **IndepGP05**. It appears that having a co-payment system on medicines may result in a more customised prescription for the patient.

An unforeseen concept that arose from the GP interviews was the suggestion of the potential introduction of a co-payment system attached to GP surgery visits for medical card holders. Medical card holders currently avail of unlimited GP surgery

visits free at the point of access. This was first alluded to by a pharmacist in the early stages of the data collection phase:

“...if the patient had a medical card and had to pay €5 to see the doctor or €10 to see the doctor, they’d see something then....” FranCP09.

When interviewing subsequently commenced with GPs, this idea was something that materialised through many indirect quotations where eventually one GP concisely summarised the issue:

“I think we are heading towards free GP care and free medication which I don’t necessarily agree with.....GPs would be in favour of advocating for co-payment both for medication and attendance of surgery visits” IndepGP06.

As there is an ongoing general practice crisis with over 26 communities in Ireland without a GP (371), the potential introduction of a co-payment system attached to GP surgery visits for medical card holders could prevent unnecessary consultations and thus would alleviate current GP capacity strains.

6.7 Discussion

This exploratory study provides a range of insights into HCP views on GMS pharmaceutical policy change over the last decade. What was evident from this analysis is that all participants, in some manner, think the GMS prescription medicine co-payment system is a good idea. However, the pharmacist cohort state they do not want to be an *“organ of revenue collection”* for the GMS co-payment. This tends to result in various losses of productivity that are not remunerated. Indeed, this financial

loss is much more than not being able to retrieve the levy. It is felt in the form of loss of staff productivity where administration workload and procedures have dramatically increased. In addition, it appears that the current information technology (IT) systems are not fit for purpose with respect to GMS co-payment retrieval. Financial losses suffered by pharmacists are also brought about by the absence of family unit linking on IT software systems in the pharmacy setting. For example, one family might pay the GMS co-payment cap of €20 for medicines per calendar month. However, because of poor IT systems communication, it is not recognised that the individuals in the family, who form a family unit, all fall under the same GMS co-payment cap, therefore the PCRS will deduct the €20 co-payment cap for each individual instead of for the family unit each calendar month. This results in financial loss for the pharmacist. This is something which needs to be rectified between the PCRS and primary care IT system providers. From the data, pharmacists would be happy to be removed from their current role in the co-payment retrieval transaction. As the GMS co-payment essentially is a tax, it could be argued that patients should deal directly with the tax collector/revenue commissioner regarding the payment of this levy as is done with other forms of taxation. Alternatively, pharmacists may be remunerated for co-payment collection, or at the very least, not financially penalised when they are unsuccessful at co-payment retrieval as is currently the case. The literature is sparse on this topic and further research is required.

Like in some western European countries (105, 372), publicly insured patients in Ireland including those aged over 70, those under 6 years, and carers avail of GP visits, free at the point of access (6). An unexpected finding from this study was that GPs

have suggested that a co-payment policy be attached to GMS patient-physician consultations that occur in their medical surgeries to prevent unnecessary overuse of this free saturated service (371). This finding indicates that overburdened GPs are aware of the concept of moral hazard and are proposing potential solutions on how to handle increasing demand on healthcare services. More European countries are attempting to or already have put policies like this in place for publicly insured patients (105). For instance, patients aged 20 years or older on the public health insurance scheme in Sweden must provide a mandatory co-payment of approximately €10 to a front desk receptionist per primary care physician visit (373). Although subtleties exist across different Swedish regions, in general, the co-payment is seen as an income to the primary care centre, and this will be considered when funds are distributed from the regional government to each local care centre. In the Czech Republic, the evidence reveals that doctor visit co-payments do not impact the number of children's doctor visits (374). However, before such a policy could be implemented in Ireland, the fee for this co-payment would have to be carefully selected. Some research has found that prescription medicine co-payments could potentially affect the number of doctor visits (375) especially higher co-payment fees which may reduce healthcare service utilisation mainly because of a demand reduction by poorer patients (376). Thus, more in-depth investigation is required to determine the optimal co-payment fee per patient-physician consultation in primary care; how best this fee could be retrieved in practice; and if the introduction of this co-payment would adhere to Sláintecare policy.

It appears that GMS co-payment policy has a ripple effect on the LTI scheme pharmaceutical policy. HCPs and others have recommended that GMS patients with

an eligible LTI, as classified by the HSE, avoid paying the co-payment by switching to the non-means-tested LTI scheme. Although the dispensing fees paid to community pharmacies for both GMS and LTI reimbursement schemes are equivalent (5), this switching of schemes creates extra administrative burden elsewhere in the health system. It results in patients straddling two medication schemes at pharmacy level. Patients get their LTI-related medicines free of charge while concomitantly using the GMS scheme to retrieve their non LTI-related medicines. This led to discussion from interviewees on the complexity of the whole medicine reimbursement system in Ireland and the associated co-payments where over 20 such schemes exist in the primary, secondary and tertiary care settings (5, 377). One HCP summarised the medicine reimbursement system and the GMS scheme co-payment quite nicely *“Even saying this out loud sounds absolutely ridiculous, you know, because if you landed from Mars and you said, ‘I’ve got an idea for a tax (co-payment fee)’, nobody would think that this was credible”* **IndepCP11**.

6.7.1 Limitations

This study was not without its limitations. Access to the total number of patients that each medical practice serves, and which proportion of those patients were medical card holders, was unattainable. Such information could have been useful in drawing conclusions between the socioeconomic differences of different patient groups. Recruitment of participants was conducted between January 2018 and April 2019. Arguably, the data collection could process could have been quicker but the primary researcher (GOB) was involved in multiple ongoing research projects at the time.

As mentioned in the methods section, an initial core set '*convenience sample*' was used for data collection. Concerns regarding selection bias in recruitment were reconciled by the fact that the sample obtained was representative of the practising HCP population. Pilot interviews were excluded from the data analysis. Although valid interviews, the interviewers felt their interviewing techniques at this early stage may have influenced participants' responses. Securing interviews with GPs proved more difficult than with pharmacists which resulted in disproportionate numbers between the groups. However, an approximately equal amount of pharmacist quotations and GP quotations are reported in the results section of this paper in an attempt to further minimise selection bias.

At the time of data collection, the main interviewer was a research pharmacist and the second interviewer was a final year pharmacy student, thus there was a possibility that participants gave socially desirable responses. This bias was difficult to eliminate as the research team felt that by disclosing their backgrounds to interviewees, an element of professionalism could be introduced into the interviews. However, given that participants were also HCPs, and practising much longer than both interviewers, it was believed that the interviewers established a solid rapport with participants where socially desirable answers did not feature dominantly in the results.

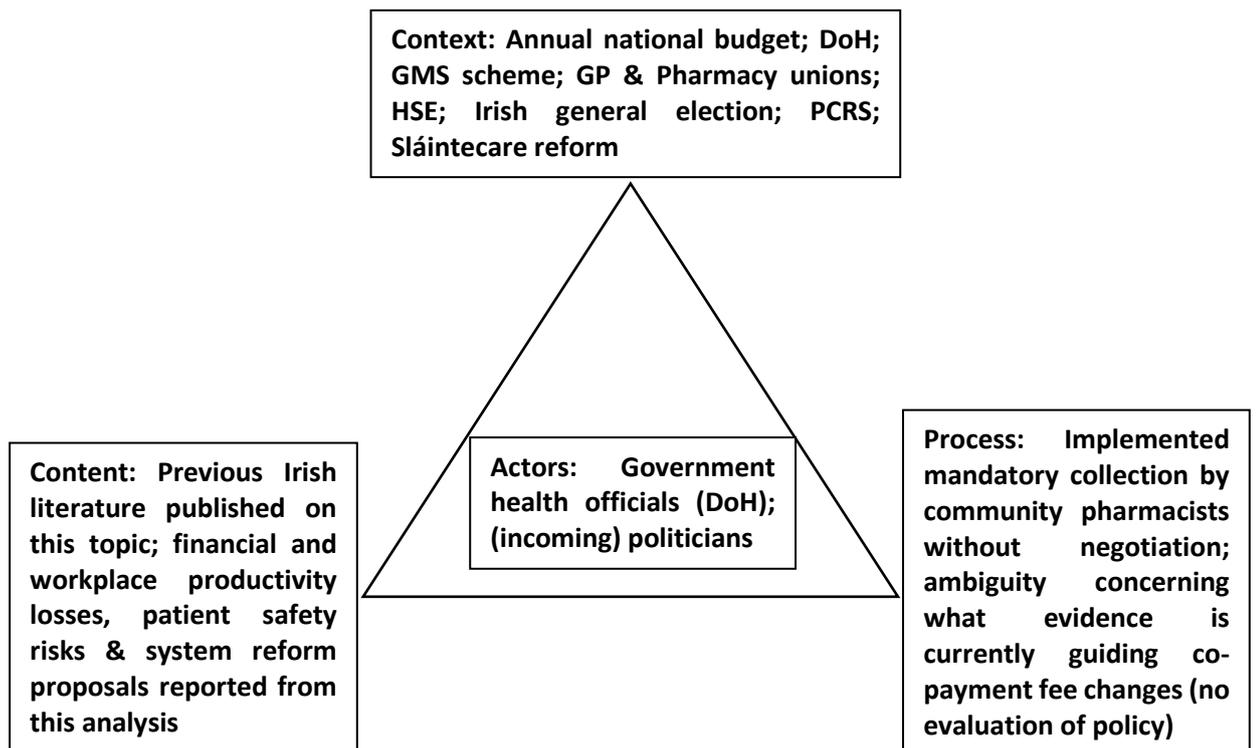
From 1st April 2019, around the same time data collection had ceased, the prescription charge decreased to €1.50 per GMS prescription item for people aged 70 years and over, up to a maximum of €15 per month per person or family unit (378). For people aged under 70 years, the prescription charge remained at €2, up to a

maximum of €20 per month per person or family unit. Therefore, it is believed that this co-payment change did not affect the study results. Furthermore, in October 2019, the Department of Finance announced that a €0.50 reduction per GMS prescription item for all medical card holders will come into effect in July 2020 (379). This research was originally intended to be part of a mixed methods study where the overall aim was to determine the impact of altering prescription charges on patient adherence to medicines on the GMS scheme in Ireland. The quantitative study planned to measure changes in adherence in essential and less-essential medicines (341, 380) pre- and post-GMS co-payment changes. However, access to national PCRS data (381) required for said analysis is only available to select research institutions.

6.7.2 From evidence to policy

This is the first study to investigate HCP stakeholder involvement in co-payments attached exclusively to prescription medicines, where recommendations from the COREQ statement were implemented to ensure that this analysis presents a transparent high-quality evaluation. It was unclear to the HCP interviewees what evidence is guiding these GMS co-payment fee changes. GMS co-payment changes are usually announced around general election time by contesting politicians or on national budget day by Government officials, unaccompanied by any solid evidence of what impact such increases or decreases can have. Previous iterations have yielded reductions in adherence to essential medicines, including anti-depressant medications with a large decrease of -10.0% (355). Reduction in the use of essential medicines results in worsening patient adherence, leading to poorer health outcomes and increased usage of health services (382-384). Given the recent flippant GMS co-

payment increases, this pharmaceutical policy appears to be more about generating revenue rather than preventing moral hazard and positively influencing prescribing patterns. If Ireland's ten-year Sláintecare plan for whole health system reform through political consensus is going to be implemented successfully, then healthcare policymakers need stakeholder buy-in to ameliorate existing pharmaceutical policies like this. In this study, both community pharmacists and GPs have suggested that their respective representative bodies should be more involved in the policy formation stages, not the post-implementation stages. Sláintecare represents a unique opportunity for all key stakeholders including policymakers, HCPs and patients to collaborate and provide input into a healthcare system that works for all. **Figure 6.2** briefly summarises the content, context and process underpinning this pharmaceutical policy using the HPT framework (46).



Key: DoH: Department of Health; GMS: General Medical Services; GP: General Practitioner; HSE: Health Service Executive; PCRS: Primary Care Reimbursement Services

Figure 6.2 Walt and Gilson policy triangle model depicting the related factors pertaining to the pharmaceutical policy

6.8 Conclusion

The GMS co-payment has undergone various iterations in recent times. Previous studies have examined its impact and sought to retrieve *'the optimal co-payment'* which concomitantly prevents medicine wastage and acts as a revenue stream (351, 355). This study too implies that there is no optimal co-payment fee as far as patients and HCPs are concerned; GPs and pharmacists did seem to favour a lower amount. Perhaps healthcare policymakers should formally evaluate the fee value every few years to see if a change is warranted. However, given all the interrelated components,

as portrayed by the HPT framework, that influence the pharmaceutical policy, this would not be a straightforward task. Indeed, this study comes at an important time as the Irish healthcare system undergoes major political, economic and health policy reform under the Sláintecare policy (23). Through political concord, the Irish Government are aiming to reorient the health system *'towards integrated primary and community care, consistent with the highest quality of patient safety in as short a time-frame as possible'* (21, 385). This study has provided a platform for experienced primary care HCPs to express their views and accounts of the Irish GMS co-payment system. For the most part, HCPs agree that there is merit to having a nominal charge attached to prescription medicines on the GMS scheme. However, participants have highlighted outstanding issues that need to be optimised in order to ameliorate primary healthcare practices and procedures (304, 386). With respect to Lewin's basic change theory model of unfreezing, changing, and refreezing (387), healthcare policymakers responsible for implementing the ten-year Sláintecare reform can bypass the unfreezing stage of this contemporary pharmaceutical policy. Both community pharmacists and GPs want to see their representative bodies more involved in supporting evidence-based policy decisions.

7 Chapter 7 Discussion

7.1 Chapter description

The research in this thesis analysed local, regional and national healthcare policy change within different Irish healthcare settings over the last decade with regard to (i) development processes, (ii) evidence generation, (iii) implementation, and (iv) outcomes using the HPT framework. This chapter is an interpretation and discussion of the key findings presented in the individual study chapters presented within the thesis. Initially, key findings of each individual study chapter were summarised and followed by a description of the implications of the research for policy decision-making. Subsequently, strengths and limitations of the research were identified. Finally, recommendations for future research and concluding remarks were provided.

7.2 Summary of findings

An objective of this thesis was to formally review the recent international literature in relation to the HPT framework. The narrative literature review (Chapter 2) sought to explore and summarise the application of the HPT framework to health-related (public) policy decisions from January 2015 to January 2020. The review identified that most health policies were positioned at national or international level mostly in lower to upper-middle-income countries and primarily concerned public health issues. It emerged that the HPT framework was commonly applied to health-related policy decisions which concerned:

- i. health human resources, services and systems
- ii. communicable and non-communicable diseases
- iii. physical and mental health
- iv. antenatal and postnatal care

While it was found that that the HPT framework was used ubiquitously in the literature to analyse a large number of health-related issues mostly positioned at national or international level, further research was required to seek an in-depth understanding of the application of the HPT framework to health-related policy decisions at a local/regional level, and to discern any potential benefits in doing this. Thus, the overarching aim of this thesis was to analyse local, regional and national health policy change within different Irish healthcare settings over the last decade using the HPT framework. Based on this, several research objectives were developed and addressed. See **Figure 1.2** repeated below for a diagrammatic depiction of how these questions sit under one overarching aim and how they relate to one another.

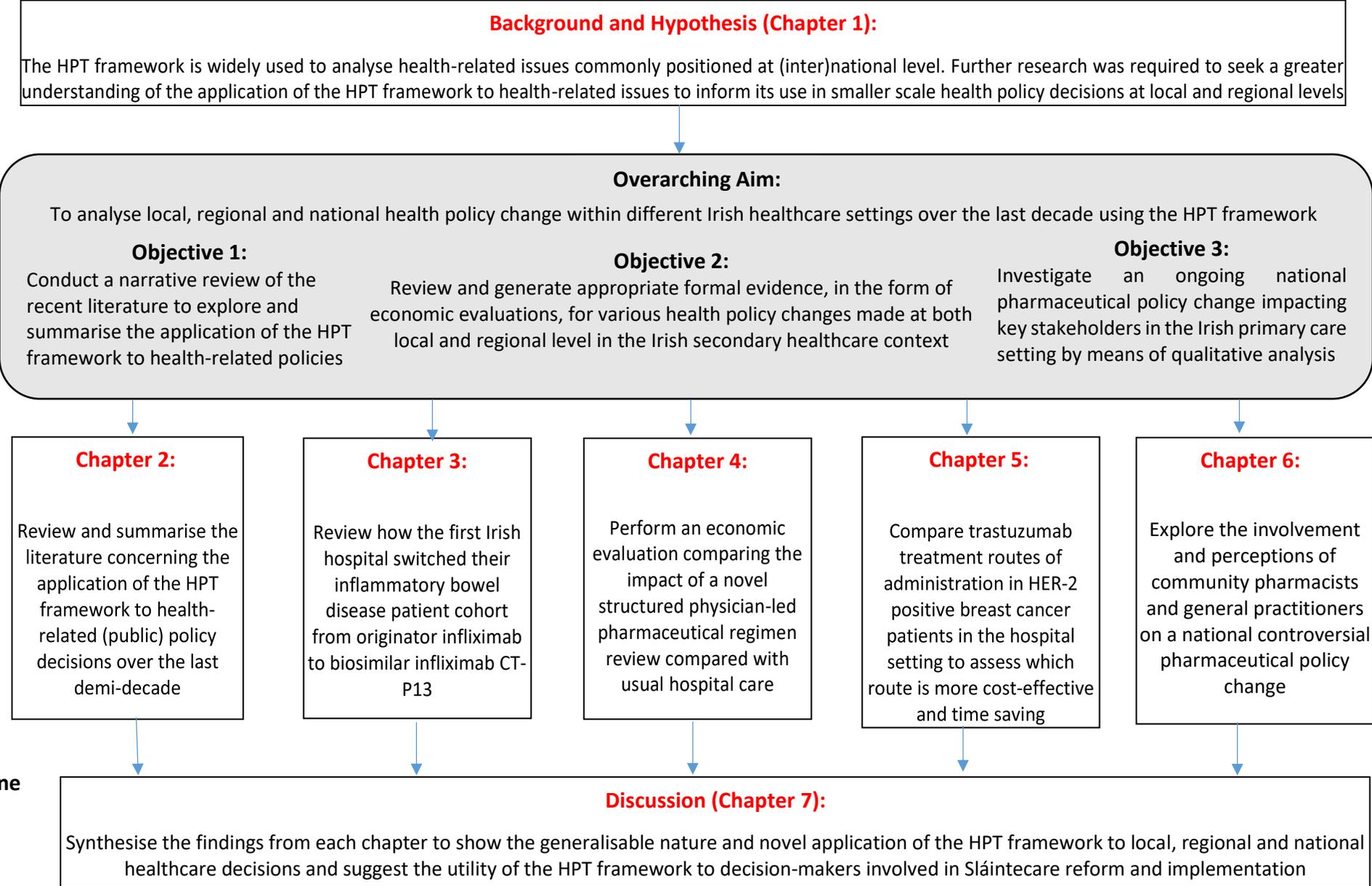


Figure 1.2
Thesis outline

The chapter concluded that given the generalisable nature of the HPT framework, future research which uses this framework in smaller scale health policy decisions at local and regional levels, could be beneficial. This conclusion fueled the thought process behind subsequent research chapters.

Following on from Chapter 2, another literature review (Chapter 3) successfully applied the policy triangle model, as a scaffolding framework, to help describe how emerging evidence was used by a large acute Irish teaching hospital to permit the introduction of biosimilar infliximab CT-P13, for the treatment of IBD, into routine care in a safe and timely manner (341). The application of the policy triangle model to similar medicine-related policies is common in the literature; the framework has been used in studies that explore medication safety concerns (94), herbal medicine regulation (96), and HPV vaccination (99, 129). The review of this local policy decision (Chapter 3) concluded that there was a significant time lag between regulatory approval and clinical acceptance given that the EMA had granted market authorisation for biosimilar infliximab CT-P13 three years prior to the initiation of this hospital's switching process (341). Another finding from Chapter 3 was the actors remarked that with the existential concern and uncertainty still surrounding the clinical use of biosimilar medicines, a distinct and individualised approach for biosimilar medicine implementation is required. However, while the MMP biosimilars initiative are doing pioneering work in this field by publishing prescribing and cost guidance to support clinicians in the prescribing of these medicines (206), the national biosimilar medicines policy referred to in Chapter 3 has yet to be published by the DoH (at time of writing – August 2020). Across European countries, differences exist in biosimilar policies, leading to variations in uptake of biosimilars and

divergences in savings all over Europe (388). Internationally, the Nordic countries, as well as some health districts in the UK, have attained victory when it comes to the switching and substitution of biosimilars. Success of the use of biosimilar infliximab CT-P13 at University Hospital Southampton (220, 221) and in Norway and Denmark has been observed, where after two years since its introduction, biosimilar infliximab reached market penetration levels in excess of 90% relative to the originator medicinal product (as of April 2016) (222). Such uptake resulted in substantial drug acquisition cost savings and subsequently increased patient access to the biosimilar medicine (188, 220). A recent study involving IBD patients in Finland showed that switching to biosimilar infliximab has no significant impact on health-related quality of life or disease activity, while reducing costs by two thirds (389).

In Chapter 4, the cost-effectiveness of physicians applying the STOPP/START (version 1.0) screening tool to older hospitalised patients with multimorbidity and polypharmacy compared with standard of care in a large acute Irish teaching hospital was evaluated by conducting a secondary analysis of RCT data (390). This study demonstrated that on average, the intervention arm was more costly but was also more effective. Compared with usual care (control), the intervention was associated with a non-statistically significant increase of €877 (95% CI –€1,807, €3,561) in mean healthcare cost, and a statistically significant decrease of –0.164 (95% CI –0.257, –0.070) in the mean number of ADR events per patient. The associated ICER per ADR averted was €5,358. The probability of the intervention being cost-effective at threshold values of €0, €5,000 and €10,000 was 0.236, 0.455 and 0.680 respectively. The physician-led intervention was deemed not likely to be cost-effective compared with usual hospital care (390). In contrast, other studies have shown that when a

pharmacist replaces the role of the physician, the outcome is more likely to be cost-effective (246). In addition, a recent systematic review concluded that computerised interventions are associated with a significant reduction in PIP in older hospitalised patients (269). Computerised interventions in this setting appear to reduce cost (270) and prove cost-effective (271). Indeed, the literature appears to suggest that pharmacists, in association with computerised CDSS, employed to carry out such medication reviews may be a more cost-effective approach (265). Within the context of this thesis, the HPT framework was used to describe how this local level policy decision concerning the physician-led STOPP/START intervention was not implemented but that the generated economic evidence contributes to the evolving STOPP/START criteria policy formation, growth and future evaluation. The policy triangle model has been cited in similar health-related interventions like a maternal health intervention (75) and a skilled birth attendance intervention (124).

In Chapter 5, two large acute University teaching hospitals at regional/provincial level comprised the study population. Similar to Chapter 4, evidence was synthesised in the form of an economic evaluation to inform policy process development. The regional policy decision concerned whether trastuzumab SC treatment should replace trastuzumab IV treatment for HER2-positive breast cancer patients in routine clinical practice (385). A prospective observational study in the form of cost minimisation analysis constituted study design and was used to assess which route was more cost-effective and time saving in relation to active HCP time. On average, the total HCP time saved per trastuzumab SC treatment cycle relative to trastuzumab IV treatment cycle was 59.21 minutes. Time savings in favour of trastuzumab SC resulted from quicker drug reconstitution, no IV catheter installation/removal, and

less HCP monitoring. Over a full treatment course of 17 cycles, average HCP time saved accumulated to 16.78 hours. In fact, this time saving of 79% is believed to be the highest recorded active HCP time saving where other studies report time savings of 51% in Spain, 48% in Canada and Russia, 36% in France, 31% in Denmark and 15% in Switzerland (322). Greater available HCP time could result in improvements in the quality of care, with more time free for monitoring, for other relevant medical duties, or indeed for providing patient information or comforting. In addition, by utilising trastuzumab SC in the place of trastuzumab IV, a saving of €596.70 per patient in active HCP time for a full 17-cycle treatment was gained. This result is consistent with those from international studies (323-326). Loss of productivity for patients receiving trastuzumab IV (2.15 days) was greater than that of trastuzumab SC (0.60 days) for a full treatment course (385). The HPT framework was used to describe the various contributing components which led to the replacement of trastuzumab IV by trastuzumab SC in clinical practice and how this contemporary policy is still evolving especially since the introduction of biosimilar trastuzumab IV to the market. The use of the policy triangle model in similar medicine-related policies is frequently observed in the literature (94, 96, 99, 129). More Irish hospitals are beginning to use trastuzumab SC, and following its successful implementation in Europe, Oceania and South America (310, 331, 338), it is envisaged that this formulation will penetrate the North American oncology landscape next. It has yet to be seen what impact biosimilar trastuzumab IV will have on the Irish and international markets and indeed how it will affect trastuzumab SC market penetration.

In Chapter 6, a qualitative interview study of Irish HCPs was conducted. The study explored the involvement and perceptions of community pharmacists and GPs on a

national pharmaceutical policy change concerning mandatory co-payments attached to prescription medicines on the Irish public health insurance scheme (391). Chapter 6 showed that both community pharmacists and GPs accepted the theoretical concept of a co-payment attached to the GMS scheme as they felt it prevents moral hazard. However, there were multiple references to the burden that the current method of co-payment collection places on community pharmacists in terms of direct financial loss and reductions in workplace productivity. GPs independently suggested that a co-payment system introduced in their field of practice may inhibit moral hazard by GMS patients in the utilisation of GP services. More European countries are attempting to or already have put policies like this in place for publicly insured patients (105). For instance, patients aged 20 years or older on the public health insurance scheme in Sweden must provide a mandatory co-payment of approximately €10 to a front desk receptionist per primary care physician visit (373). Although subtleties exist across different Swedish regions, in general, the co-payment is seen as an income to the primary care centre, and this will be considered when funds are distributed from the regional government to each local care centre. In addition, it was unclear to both community pharmacists and GPs in this research chapter what evidence is guiding the GMS co-payment fee, or changes to the policy over time (391). However, such iterations have yielded reductions in adherence to essential medicines, including anti-depressant medications with a large decrease of -10.0% (355). Reduction in the use of essential medicines results in worsening patient adherence, leading to poorer health outcomes and increased usage of health services (382-384). The HPT framework was used to depict the interrelated factors which underpin this national pharmaceutical policy. Going forward, both community

pharmacists and GPs have suggested that their respective representative bodies should be more involved in the policy formation stages, not the post-implementation stages (391). Similarly, a recent study that examines the implementation of out-of-pocket payments to GPs in Denmark applied both the HPT framework and Kingdon's multiple streams theory in its policy analysis (105). It found that the potential introduction of out-of-pocket payments in Denmark may lead to decreased health expenditure, but also increased inequalities.

7.3 From evidence to policy

The principal contribution of this thesis has been the novel and successful application of the HPT framework to diverse local, regional and national healthcare decisions in the Irish context which exemplifies the generalisable nature of the policy triangle model. This demonstration bears significant relevance for the Irish healthcare system at present given that Sláintecare is officially underway (21). The Sláintecare Programme Implementation Office refined the implementation strategy (which contained 106 sub-actions) into a programmatic action plan in 2019 (22). This is the first of many action plans and will be updated annually during the ten-year implementation period. The author of this thesis proposes that the HPT framework should be used in the analysis *of/for* policy in the myriad of upcoming health policies to be made and reviewed under Sláintecare reform in its future action plans. This framework can have a notable impact on local, regional and national health policy analysis reform if implemented in Sláintecare decision-making. Other countries like Iran and Ghana have already used the HPT framework when exploring potential

issues and policies surrounding the similar aim of UHC facilitation in their primary healthcare settings (79, 98). In addition, the robust economic and qualitative evidence generated over the course of this thesis will assist other local and regional healthcare payers and interested parties to objectively determine whether it is worth pursuing and examining a respective health policy relevant to them.

Evidence produced and reviewed in the thesis has and will influence healthcare policy decisions, through conference publication nationally and internationally and through peer reviewed publications. Fortunately, implementation of the some of the proposed health policy decisions investigated throughout Chapters (3 - 6) will not require a substantial investment. However, the reallocation of funds for additional employment or additional payment of services, in addition to agreement of all stakeholders involved in the provision of care to the relevant patient group, may be challenging.

While dissemination of research through the medium of academic journals and conferences is an important aspect of any research thesis, communication through these channels may not be reaching the correct audience if one wants to see research influencing policy at local, regional and national levels. It is vital that if this research is to make an impact, it is brought to the attention of key decision-makers within the healthcare system. The author of this thesis has ensured that throughout the course of the research, engagement with the wider health policymaker community was made. This thesis resulted in collaboration with four major teaching hospitals, independent and franchise community pharmacies, and independent GP medical surgeries.

In addition, on October 18th, 2018, the published paper which underpinned Chapter 3 was submitted to the HSE-Medicines Management Programme in response to their national '*best-value biological medicines*' consultation (206); parts of the published paper helped inform version 2.0 of the '*MMP roadmap for the prescribing of best-value biological medicines in the Irish healthcare setting*' document published from the consultation process (392). On July 13th, 2018, at their request, the published paper derived from Chapter 4 was submitted to the creators of the STOPP/START criteria; the developers are currently updating the STOPP/START guidelines (version 3.0) to help inform future policymaking regarding the most appropriate means of application and delivery for this screening tool. On September 25th, 2018, at the request of its Chief Pharmacist, the published paper which stemmed from Chapter 5 was submitted to the HSE-National Cancer Control Programme to inform policymaking and reimbursement on this topic. On June 11th, 2020, the published paper that comprised Chapter 6 was submitted to the DoH, the Irish College of General Practitioners, the Irish Medical Organisation, the IPU, and the Pharmaceutical Society of Ireland to inform future policymaking on the subject area.

Moreover, once this thesis is published by the Cork Open Research Archive (based in UCC), relevant segments that demonstrated the generalisable nature and novel application of the HPT framework to diverse local, regional and national healthcare decisions in the Irish context will be forwarded to the Committee on the Future of Healthcare. This will be in the guise of a policy briefing document (see **Appendix XXII**) and will highlight the framework's potential utility in future Sláintecare reform and implementation action plans.

7.4 Strengths and limitations

All research Chapters (2 - 6) outlined have generated full publications in peer reviewed academic journals (341, 385, 390, 391, 393). Additionally, research has been presented at multiple conferences in both poster and oral format (see **Appendix III**). While publication is not the definitive goal for investigating a problem, it is one metric that reflects the impact of this thesis overall and the interest in the topics from the wider academic community. The author adopted a proactive approach to ensuring that a wider and lay audience was made aware of any work undertaken by publishing blogs (see **Appendix I**) and a policy brief (see **Appendix XXII**).

The research findings presented in this thesis use the HPT framework to help describe, examine and understand various health-related policy decisions. Frameworks like the policy triangle model are systematically used to organise inquiry for theory generation through identifying elements and relationships among these elements (96, 105, 127). Other frameworks for examining policy (394) and theories of the policy process (40) were considered to be more narrow in scope, focusing on either the contents of policy or the actors/processes and requiring specific information beyond that which would be commonly provided/available.

As mentioned, analysis *of* policy is the most accurate way to describe the use of the HPT framework throughout research Chapters (3 - 6). It is generally retrospective and explanatory; it looks back to explore the determination of the policy capturing how the policy got on the agenda, what the policy consisted of, who was involved and did it achieve its goals (30). In contrast, prospective policy analysis hypothesises potential opportunities for influencing the policy environment; there are few accounts in the

overall policy literature of prospective policy analysis (395). By applying the descriptive HPT framework to health-related policy decisions, it assists interested parties and invested decision-makers in interpreting the policy in question. It allows for comparison between policies that stem from different sectors of healthcare using four components (actors, content, context, process). This demonstrates the broadly applicable nature of the policy triangle model. The narrative review (Chapter 2) has already identified how the HPT framework can be applied to a wide variety of health-related (public) policy decisions such as communicable and non-communicable diseases (102, 109, 113, 128), mental health (103, 121, 132) and the provision of primary healthcare (118, 122). In addition, a recent literature review has shown that the HPT framework is widely used to understand diverse policy experiences in multiple LMIC settings, with applications that encompass both quite simple and descriptive narratives and less frequently, fuller more explanatory analysis (47). These reviews exemplify the generalisable nature of the HPT framework.

In this thesis for example, the policy triangle model provides a platform that allows policymakers to consider health policy decisions concerning biosimilar medicines (Chapter 3), medication screening interventions (Chapter 4), pharmaceutical formulation switching (Chapter 5), and co-payment charges (Chapter 6) using a common descriptive framework. If for example, a Sláintecare decision-maker had funding to invest in only one of the four policies explored throughout Chapters (3 - 6), they could quickly examine the different contributing components of each policy by comparing and contrasting the respective actors, content, context and process (see **Table 7.1**); this could help inform their decision. This action bears resemblance to cross-country comparative policy analysis studies discussed in Chapter 2 (70, 104,

141). However, the difference being that instead of examining one policy among multiple countries, multiple policies are being simultaneously evaluated in one country.

Table 7.1 Components of HPT framework from Chapters (3 - 6)

Chapter	Actors	Content	Context	Process
3	Consultant Gastroenterologist & Chief Pharmacist	Independent systematic evidence trail outlined in Figure 3.1 in Chapter 3	Irish biosimilar landscape influenced by national biosimilar policy; DoH; EMA; HPRA; IPHA; MMP; Sláintecare reform	Three-year procedure; new patients initiated; all patients subsequently switched; continuous post-switch monitoring by actors
4	Developers & Users (Geriatricians & Clinical Pharmacists) of STOPP/START criteria	SENATOR & OPERAM clinical trials; cost-effectiveness results of the Chapter 4 trial and of the SPRM with CDSS trial in same hospital	Increasing life expectancy of and healthcare expenditure on elderly as reported by OECD; NMS intervention; Sláintecare reform	Ongoing; STOPP/START criteria application being evaluated in a variety of healthcare settings involving different HCPs & CDSS
5	Consultant Oncologists & Nursing & Pharmacy Departments	HannaH, SafeHer & PrefHer clinical trials; cost savings, reduced active HCP time & decreased loss of productivity results from the economic evaluation in Chapter 5	Irish biosimilar & oncology landscape (biosimilar trastuzumab IV launch); NCCP; Sláintecare reform	Hospital 1 (Chapter 5) involvement in SafeHer trial in 2011; switching period commencement in early 2014 and late 2015; continual positive emerging clinical and economic evidence
6	Government health officials (DoH); (incoming) politicians	Previous Irish literature published on this topic; financial and workplace productivity losses, patient safety risks & system reform proposals reported from Chapter 6	Annual national budget; DoH; GMS scheme; GP & Pharmacy unions; HSE; Irish general election; PCRS; Sláintecare reform	Implemented mandatory collection by community pharmacists without negotiation; ambiguity concerning what evidence is currently guiding co-payment fee changes (no evaluation of policy)

Key: CDSS: Clinical Decision Support Software; DoH: Department of Health; EMA: European Medicines Agency; GMS: General Medical Services; GP: General Practitioner; HCP: Healthcare Professional; HPRA: Health Products Regulatory Authority; HSE: Health Service Executive; IPHA: Irish Pharmaceutical Healthcare Association; IV: Intravenous; MMP; Medicines Management Programme; NCCP: National Cancer Control Programme; NMS: New Medicines Service; OECD: Organisation for Economic Co-operation and Development; PCRS: Primary Care Reimbursement Services; SPRM: Structured Pharmacist Review of Medication

The chapters within this body of work used a variety of rich data sources to inform the overall analyses and subsequent conclusions drawn from the thesis. The findings from the qualitative analysis (Chapter 6) are based on a sample that was broadly representative of the practising HCP population. This mediates concerns regarding selection bias in recruitment. The cost-minimisation analysis (Chapter 5) was based on primary data collected for a prospective observational study. Data collection was spread over two centres which provided a larger data pool. The cost-effectiveness analysis (Chapter 4) was based on primary data collected for a RCT. This enabled the accurate identification of resource use associated with both intervention and control arms. Chapter 3, a review into how emerging evidence was used by a large acute Irish teaching hospital to permit the introduction of biosimilar infliximab CT-P13 for the treatment of IBD into routine care, was informed by a literature review consisting of published studies, reviews, reports, position statements, articles, clinical guidelines and recommendations from national bodies, regulatory authorities and professional organisations (341). By including both formal and informal literature in the Chapter 3 review, this facilitated a thorough appraisal of how this biosimilar policy change came to fruition in a large acute Irish teaching hospital at local level.

Each research chapter was subject to extensive methodological rigour. The trial-based economic evaluation (Chapter 4) adopted the CHEERS guidelines as guidance for reporting the research in the paper write-up (259). In addition, the methodologies used are highly suitable for use alongside cluster RCTs (255); the use of multi-level mixed effect models is an appropriate method of evaluating clustered data. The manuscript published from Chapter 5 also adopted the CHEERS guidelines for reporting (259). The research published from Chapter 6 abided by the COREQ

guidelines (370). The qualitative data in Chapter 6 was analysed using the Framework Approach (55). This method originated in large-scale social policy research but is becoming an increasingly popular approach in medical and health research (64) making it highly suitable for analysis of qualitative data like that gathered for use in Chapter 6 and for use in health policy analysis.

Individual chapters elaborate on the specific limitations of each study in the '*Discussion*' sections. However, it can be argued that Chapter 4 underwent more analysis than the others and thus some additional limitations are noteworthy. For example, while trial-based economic evaluations (Chapter 4) are an established and relevant form of assessment, they do give rise to their own methodological challenges including choice of comparison therapy; measurement in trials versus routine practice; intermediate versus final health outcome; inadequate patient follow-up; protocol driven costs and outcomes (54). In addition, while the datasets used were considered trustworthy and generally complete, all datasets where data are manually collected and compiled tend to have some degree of missing data. Depending on the degree of missingness and significance of the missing variable(s), such omissions could potentially systematically bias the analysis. However, missing/censored data were not an issue in the evaluation, as follow-up was facilitated by a unique hospital number identifier and confined to a single centre over a short time period. Moreover, in the case of the medication review research (Chapter 4), the trial follow-up period was shorter than the period during which differences in health effects and use of healthcare resources between interventions persist; increasing the uncertainty surrounding whether investing in this intervention would be a good use of healthcare resources over a longer period of time.

Furthermore, the research (Chapter 4) was predominantly incorporated around retrospective evaluation of data sources or as an add-on to previously completed clinical trials; reductions in uncertainty surrounding some of the input such as HCP time estimates data could have been reduced through earlier engagement with primary researchers. However, scenario analyses were conducted to account for this uncertainty (390).

Although the research that uses the HPT framework presented within this thesis does have some exploratory or investigative aspects, it is largely descriptive in nature, thus lacking an analytical focus. The main question the model often asks is '*what happened*' and not '*what explains what happened*'. So, while the HPT framework is useful to think systematically about all the different factors that might affect policy, it is a highly simplified representation of a complex set of interrelationships which gives the impression that its four components can be considered separately (30); they cannot. Indeed some research has suggested that the triangle model pays too little attention to other factors that explain why and how policies change (396, 397).

The research within this thesis focuses on experience around separate respective policies in one country (Ireland) at one time point, rather than comparing and contrasting experience across countries or over time, between health policies or across sectors within a country, or between implementing units and people/patient groups. While it is reported that the consistent application of the HPT framework across polices from different health systems can enhance the reliability of cross-country comparisons (70, 104, 398); it is a possibility that the substantive findings from this thesis may not be generalisable to other international health settings. This

is potentially owing to Ireland's distinctive ethnicity and political situation which underpins the content and context components of the HPT framework used to describe the health-related policy decisions outlined in Chapters (3 - 6). This distinctive political situation was described in Chapter 1 where, for example, Ireland is the only country in western Europe that does not offer universal access to primary care (4). However, the methodology of applying the HPT framework to health-related policy decisions at local and regional level is not restricted by geography or health system infrastructure.

For the purposes of this research, distinct health-related policies made in various health sectors at local, regional and national levels in Ireland were deliberately chosen for the application of the policy triangle model; this helped address the overarching aim and sub-objectives of the thesis. But in practice, more explicit use of formal case study analysis approaches is observed. For example, appropriate case selection criteria must be established, each case must be adequately contextualised, and efforts must be made to deliberately identify and explain unusual experiences and findings (399).

Political context was considered through the medium of Sláintecare. However in reality, the political contexts described in Chapters (3 - 6) for each health-related policy decision may be much more complex than illustrated. There could be power play and politics involving actors at local, regional and national level where such a milieu may not be captured in the presented research. The influence of power and actor relations is commonly cited in the literature (400, 401). Stakeholder analysis can be used to help understand about relevant actors, their intentions, interrelations,

agendas, interests, and the influence or resources they have brought or could bring on decision-making processes during policy development (52). The use of stakeholder analysis could have been used in this thesis to complement the HPT framework policy analysis approach as is sometimes seen in the literature (92, 107, 139, 141). However, given that most health-related policies explored throughout this thesis were positioned at local and regional level, it is believed that a stakeholder analysis would contribute no additional benefit to the description of the policies in question.

The process of policymaking refers to the way in which policies are initiated, developed or formulated, negotiated, communicated, implemented and evaluated (30). The most common approach to understanding policy process is to use the stages heuristic model (37). The process component for each health-related policy decision in Chapters (3 - 6) was largely descriptive in nature thus not explored extensively. However, given that these policy decisions were looked at a local and regional level, the formal steps of development through to implementation can often be bypassed quite quickly. By generating an understanding of the factors influencing the experience and results of policy change, such analysis can inform action to strengthen future policy development and implementation. However, as mentioned in specific chapters, some policy decisions are still in development and the nature of their respective process will evolve over time. Further research may formally document their process journey and should investigate the use of explanatory policy process theoretical frameworks such as the Kingdon's multiple streams theory or ACF (44). This would ensure an in-depth analysis, evaluation and critique of unique policy dynamics.

7.5 Future research

There are many interpretations from the research findings presented in this thesis. Chapter 2 identified that the types of health policies analysed using the HPT framework were almost all positioned at national or international level mostly in lower to upper-middle-income countries and primarily concerned public health issues. Following this finding, Chapters (3 - 6) successfully investigated different health-related policy decisions at local, regional and national level in a high-income country (Ireland) using the policy triangle model. Its successful application to smaller scale health policy decisions represents one of the novel aspects of this thesis. It is evident that the HPT framework is not confined to any one setting or to a particular type of health-related policy decision. Although not investigated in this thesis, further applications using the policy triangle model as a descriptive framework in policy arenas outside health could be explored.

The current interest in health policy and systems research provides exciting opportunities for the field, but also brings the threat of disciplinary capture by the clinical, biomedical, and epidemiological disciplinary perspectives dominant in wider health research (402). Health policies are complex social and political phenomena, constructed by human action rather than naturally occurring (402). As the health policy field continues to grow, it is crucial that all perspectives on health policy issues, from social science to epidemiology, are respected; this will ensure that an interdisciplinary understanding is built into all health policy analysis approaches.

The use of the Walt and Gilson policy triangle model in this thesis provided a rich descriptive analysis and narrative of the development of various health-related policy

decisions in Ireland. This was useful in highlighting how policy issues emerged, how they were developed and what current status they hold. To enhance understanding of the policy dynamics, future research would comprise of an explanatory analysis using one or more policy process theoretical frameworks such as the ACF (38), the Kingdon's multiple streams theory (39), the punctuated equilibrium framework (40) and the institutional analysis and development framework (40).

A myriad of policy frameworks and theories exists (31). The burgeoning literature of health policy analysis sees novel policy frameworks being developed quite frequently with the '*policy cube*' approach being the latest addition (36). While it is great to observe such advancements in the field, having too many choices of frameworks can potentially complicate the selection process. The research from this thesis has illustrated how generalisable and adaptable the application of the HPT framework is to health-related policy decisions of almost any nature in various settings. Given this advantage, the author of this thesis would like to see the policy triangle model used by the Committee on the Future of Healthcare who steer Sláintecare implementation. By standardising the approach to health policy analysis during this ten-year reform period by using a common framework, health-related policy decisions have the potential to be made more easily and readily thus ensuring successful fruition of Sláintecare goals (see **Appendix XXII**).

7.6 Conclusion

Overall, many beneficial health-related policy decisions are being made at local, regional and national levels that add/remove substantial value to/from the Irish

healthcare system. These policy decisions, driven by actors, often result in economic and clinical benefits for health service providers and patients alike. This thesis has contributed to the overall evidence base surrounding the various health-related policy decisions explored throughout. It also has successfully demonstrated that, notwithstanding the setting or nature relating to a particular health policy, it is possible to compare and contrast wide-ranging health policies using the HPT framework thus fulfilling the overarching thesis aim. In the past, much of the valuable health policy research produced was regularly considered within the scope of its own field without the ability to easily make comparisons with other health policy research stemming from different subject areas. Using assorted health policies from different healthcare settings in Ireland over the last decade, this thesis has overcome a large element of the knowledge deficit by demonstrating that the generalisable nature of the policy triangle model allows for comparing and contrasting of health policies that come from almost any health-related field.

However, this finding will prove ineffectual unless acted upon and alerted to relevant health policy actors. Sláintecare reform proposes the establishment of a universal, single-tier health service where patients are treated solely on the basis of health need; the reorientation of the health system '*towards integrated primary and community care, consistent with the highest quality of patient safety in as short a time-frame as possible*'. To promise the delivery of such major policy change to a national health system over a ten-year period requires that consideration be given to the application of a common framework that can be used by all decision-makers when conducting the relevant required health policy analysis.

Research and evidence presented throughout this thesis has shown that despite limitations, the generalisable and adaptable nature of the policy triangle model demonstrates that it could be used as a common descriptive framework to assist with health policy analysis under Sláintecare reform plans. By each relevant decision-maker applying the same model to all health-related policy decisions, the Sláintecare implementation process could proceed more quickly and effectively to the benefit of the people of Ireland.

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8 Appendices

8.1 Appendix I – All publications

Citation	Peer reviewed journal	Authorship status
Full-text publications:		
<p>“Cost Effectiveness Analysis of a Physician-Implemented Medication Screening Tool in Older Hospitalised Patients in Ireland” Gary L O’Brien, Denis O’Mahony, Paddy Gillespie, Mark Mulcahy, Valerie Walshe, Marie N O’Connor, David O’Sullivan, James Gallagher, Stephen Byrne (2018) <i>Drugs & Aging</i>, DOI:10.1007/s40266-018-0564-0</p>	Drugs and Aging	1 st
<p>“Biosimilar Infliximab Introduction into the Gastroenterology Care Pathway in a Large Acute Irish Teaching Hospital: A Story Behind the Evidence” Gary L O’Brien, Donal Carroll, Valerie Walshe, Mark Mulcahy, Garry Courtney, Stephen Byrne (2018) <i>Generics and Biosimilars Initiative Journal (GaBI Journal)</i>, DOI:10.5639/gabij.2018.0701.004</p>	Generics and Biosimilars Initiative Journal (GaBI Journal)	1 st
<p>“Cost Minimization Analysis of Intravenous or Subcutaneous Trastuzumab Treatment in Patients With HER2-Positive Breast Cancer in Ireland” Gary L O’Brien, Cian O’Mahony, Katie Cooke, Ada Kinneally, Sarah-Jo Sinnott, Valerie Walshe, Mark Mulcahy, Stephen Byrne (2019) <i>Clinical Breast Cancer</i>, DOI:10.1016/j.clbc.2019.01.011</p>	Clinical Breast Cancer	1 st
<p>“Out of Pocket or Out of Control: A Qualitative Analysis of Healthcare Professional Stakeholder Involvement in Pharmaceutical Policy Change in Ireland” Gary L O’Brien, Sarah-Jo Sinnott, Bridget O’Flynn, Valerie Walshe, Mark Mulcahy, Stephen Byrne (2020) <i>Health Policy</i>, DOI:10.1016/j.healthpol.2020.02.011</p>	Health Policy	1 st
<p>“Health Policy Triangle Framework: Narrative Review of the Recent Literature” Gary L O’Brien, Sarah-Jo Sinnott, Valerie Walshe, Mark Mulcahy, Stephen Byrne (2020) <i>Health Policy OPEN</i>, DOI:10.1016/j.hpopen.2020.100016</p>	Health Policy OPEN	1 st
<p>“Computerised Interventions Designed to Reduce Potentially Inappropriate Prescribing in Hospitalised Older Adults: a Systematic Review and Meta-Analysis” Kieran Dalton, Gary L O’Brien, Denis O’Mahony, Stephen Byrne (2018) <i>Age and Ageing</i>, DOI:10.1093/ageing/afy086</p>	Age and Ageing	2 nd
<p>“Thirst for Change in a Challenging Environment: Healthcare Providers’ Perceptions of Safety Culture in a</p>	Irish Journal of Medical Science	2 nd

Citation	Peer reviewed journal	Authorship status
Large Irish Teaching Hospital" Laura L Gleeson, Gary L O'Brien, Aoife Delaney, Denis O'Mahony, Stephen Byrne (2020) Journal of Interprofessional Care, manuscript under peer review		
"Interprofessional Communication in the Hospital Setting: A Systematic Review of the Qualitative Literature" Laura L Gleeson, Gary L O'Brien, Denis O'Mahony, Stephen Byrne (2020) Journal of Interprofessional Care, manuscript under peer review	Journal of Interprofessional Care	2 nd
"Safety Culture in a Major Accredited Irish University Teaching Hospital: A Mixed Methods Study using the Safety Attitudes Questionnaire" Laura L Gleeson, Leanne Tobin, Gary L O'Brien, Erin K Crowley, Aoife Delaney, Denis O'Mahony, Stephen Byrne (2020) Irish Journal of Medical Science, DOI:10.1007/s11845-020-02228-0	Irish Journal of Medical Science	3 rd
"A Cost Comparison Study to Review Community versus Acute Hospital Models of Nursing Care Delivered to Oncology Patients" Cian O'Mahony, Kevin D Murphy, Gary L O'Brien, Joe Aherne, Terry Hanan, Louise Mullen, Maccon Keane, Paul Donnellan, Kathleen Malee, Stephen Byrne (2020) European Journal of Oncology Nursing, DOI:10.1016/j.ejon.2020.101842	European Journal of Oncology Nursing	3 rd
Published conference abstracts:		
"Economic Analysis of a Physician-implemented, Medication Screening Tool in Older Irish Hospitalised Patients" Gary L O'Brien, Denis O'Mahony, Paddy Gillespie, Mark Mulcahy, Valerie Walshe, Marie N O'Connor, David O'Sullivan, James Gallagher, Stephen Byrne (2017) Age and Ageing, DOI:10.1093/ageing/afx145.18 - The 65th Jubilee Annual & Scientific Meeting of the Irish Gerontological Society, Wexford, Ireland, September 2017	Age and Ageing	1 st
"A Cost-Effectiveness Analysis of A Physician-Implemented, Medication Screening Tool in Older Hospitalised Patients in Ireland" Gary L O'Brien, Denis O'Mahony, Paddy Gillespie, Mark Mulcahy, Valerie Walshe, Marie N O'Connor, David O'Sullivan, James Gallagher, Stephen Byrne (2017) Value in Health, DOI:10.1016/j.jval.2017.08.533 - ISPOR 20 th Annual Congress, Glasgow, Scotland, November 2017	Value in Health	1 st
"Uptake of Seasonal Influenza Vaccination amongst a Cohort of Pharmacists in Ireland"	Value in Health	1 st

Citation	Peer reviewed journal	Authorship status
Gary L O'Brien, Susan O'Dwyer, Mairead O'Grady, Leigh Lehane, Stephen Byrne, Lisa Buckley (2018) Value in Health, DOI:10.1016/j.jval.2018.09.1397 - ISPOR Europe, Barcelona, Spain, November 2018		
"A Cost Saving Measure from the Utilisation of Biosimilar Infliximab in the Irish Secondary Care Setting" Gary L O'Brien, Donal Carroll, Valerie Walshe, Mark Mulcahy, Garry Courtney, Cian O'Mahony, Stephen Byrne (2018) Value in Health, DOI:10.1016/j.jval.2018.09.876 - ISPOR Europe, Barcelona, Spain, November 2018	Value in Health	1 st
"Cost Minimisation Analysis of Intravenous or Subcutaneous Trastuzumab Treatment in Patients with HER2-Positive Breast Cancer in Ireland" Gary L O'Brien, Cian O'Mahony, Katie Cooke, Ada Kinneally, Sarah-Jo Sinnott, Valerie Walshe, Mark Mulcahy, Stephen Byrne (2019) Journal of Oncology Pharmacy Practice, DOI:10.1177/1078155219871150 - ISOPP International Symposium, London, UK, October 2019	Journal of Oncology Pharmacy Practice	1 st
"Computerised Medication Analysis Designed to Minimise Inappropriate Prescribing in Older Hospitalised Patients: A Systematic Review" Kieran Dalton, Gary L O'Brien, Denis O'Mahony, Stephen Byrne (2017) Age and Ageing, DOI:10.1093/ageing/afx144.236 - The 65th Jubilee Annual & Scientific Meeting of the Irish Gerontological Society, Wexford, Ireland, September 2017	Age and Ageing	2 nd
"Investigating Patient Safety Culture using the Open Comments Section of the Safety Attitudes Questionnaire (SAQ)" Laura L Gleeson, Gary L O'Brien, Leanne Tobin, Erin K Crowley, Aoife Delaney, Denis O' Mahony, Stephen Byrne (2019) International Journal of Pharmacy Practice, DOI:10.1111/ijpp.12533 - Health Services Research & Pharmacy Practice Conference, Birmingham, UK, April 2019	International Journal of Pharmacy Practice	2 nd
"Measurement Health Outcomes Associated with Medicines at a National Level" James Gallagher, Muireann McAlister, Stephen Byrne, Gary L O'Brien (2019) Value in Health, DOI:10.1016/j.jval.2019.04.1164 - ISPOR New Orleans, LA, USA, May 2019	Value in Health	Senior Author Position
Other publications:		
"Biosimilar Adoption and Acceptance in Ireland – Still More To Be Done" Gary L O'Brien, Donal Carroll, Valerie Walshe, Mark Mulcahy, Garry Courtney, Blythe	Value & Outcomes	1 st

Citation	Peer reviewed journal	Authorship status
Adamason, Stephen Byrne (2018) Value & Outcomes Spotlight July/August 2018 Vol. 4, No. 4 pg 29-31, https://www.ispor.org/publications/journals/value-outcomes-spotlight/abstract/july-august-2018/biosimilar-adoption-and-acceptance-in-ireland-still-more-to-be-done	Spotlight Journal, ISPOR	
“Biosimilars Infographic – VOS By the Numbers” Gary L O’Brien, Koen Degeling, Jayeshkumar Patel, Simrun K Grewal, Blythe Adamason (2018) Value & Outcomes Spotlight July/August 2018 Vol. 4, No. 4 pg 24, https://www.ispor.org/publications/journals/value-outcomes-spotlight/issue/july-august-2018	Value & Outcomes Spotlight Journal, ISPOR	1 st
“Medication Screening of Older Hospitalised Patients: The Cost-Effective Way Forward” Gary L O’Brien (2018) SPHeRE Blog, http://www.sphereprogramme.ie/medication-screening-of-older-hospitalised-patients-the-cost-effective-way-forward/	SPHeRE Blog	1 st
“A European Cancer Plan; Make it Disruptive!” Gary L O’Brien (2019) EHFG Blog, https://blog.ehfg.org/2019/10/10/a-european-cancer-plan-make-it-disruptive-f12/	EHFG Blog	1 st
“Can People Afford to Pay for Healthcare; New Evidence on Financial Protection in Europe” Gary L O’Brien (2019) EHFG Blog, https://blog.ehfg.org/2019/10/10/can-people-afford-to-pay-for-healthcare-new-evidence-on-financial-protection-in-europe-f7/	EHFG Blog	1 st
“Can People Afford to Pay for Healthcare? An Interview with Tamás Evetovits” Gary L O’Brien, Stefano Guicciardi (2020) EHFG Blog, https://blog.ehfg.org/2020/08/17/can-people-afford-to-pay-for-healthcare/	EHFG Blog	1 st
“How Prescription Charges for Medical Cardholders Affect Patients” Gary L O’Brien (2019) RTÉ Brainstorm, https://www.rte.ie/brainstorm/2019/1203/1096674-how-prescription-charges-for-medical-cardholders-affect-patients/	RTÉ Brainstorm Public Outreach Article	1 st
“Overcoming Hurdles; Measurement of Health-Related Outcomes Associated with National Level Medicines Usage in Ireland” Gary L O’Brien, Muireann McAlister, Stephen Byrne, James Gallagher (2020) Drugs in Context, DOI:10.7573/dic.2020-4-2	Drugs in Context Editorial	1 st

8.2 Appendix II – Postgraduate taught modules completed

Module code	Module name (<i>completed as part of UCC structured PhD - compulsory requirements</i>)	ECTS
PG6003	Teaching and Learning for Graduate Studies	5
PG6008	Qualitative Data Analysis and Computer Assisted Qualitative Data Analysis Software for the Social Sciences and Humanities	5
PG6009	Graduate Information Literacy Skills	5
PG7016	Systemic Reviews for the Health Sciences	5
PG7200	External Module	10
ST6013	Statistics and Data Analysis for Postgraduate Research Students	10

Module Code	Module name (<i>completed as part of PGCert in Innovation, Commercialisation and Entrepreneurship</i>)	ECTS
AC6301	Innovation Finance	5
IS6306	Technology Business Planning	5
IS6307	Creativity and Opportunity Recognition	5
LW6104	Intellectual Property Law for High-tech Entrepreneurs	5
MG6305	People and Organisations	5
MG6705	Markets for High-tech Entrepreneurs	5

8.3 Appendix III – Training courses and conferences attended

Training course name	Location	Date attended (mm/yyyy)
HRB-TMRN Workshop on Economic Evaluations alongside Randomised Controlled Trials (1 day)	St. James Hospital	10/2016
Introduction to SPSS (2 days)	UCC	12/2016
STATA Software Training (1 day)	UCC	05/2017
Foundations of Economic Evaluation in Health Care (5 days)	University of York	06/2017
ICH Good Clinical Practice (GCP) Training (1 day)	HRB CRF-C UCC	09/2017
NVivo Software Training (2 days)	UCC	01/2018
Qualitative Research Methods of Analysis (2 days)	University of Oxford	05/2018
Advanced Methods for Cost-Effectiveness Analysis: Meeting Decision-makers' Requirements (5 days)	University of York	06/2018
Outcomes Measurement and Valuation for Health Technology Assessment (3 days)	University of York	07/2019

Conference name	Presentation	Location	Date attended (mm/yyyy)
National Centre for Pharmacoeconomics (NCPE)	None	Dublin	03/2017
All-Ireland Schools of Pharmacy Conference	None	UCC	04/2017
Irish Gerontological Society (IGS)	Oral	Wexford	09/2017
Irish Institute of Pharmacy (IIOP)	Poster	Louth	10/2017
European Drug Utilisation Research Group (EuroDURG)	Poster*	Glasgow	11/2017
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	Poster	Glasgow	11/2017
The Irish Network of Medical Educators (INMED)	Poster	UCC	02/2018
NCPE	None	Dublin	03/2018
School of Pharmacy (SOP) PhD Seminar	Oral	UCC	03/2018

Conference name	Presentation	Location	Date attended (mm/yyyy)
International Conference on Pharmacoepidemiology & Therapeutic Risk Management	None	Prague	08/2018
Hospital Pharmacists Association of Ireland (HPAI) Aseptics Special Interest Group (ASSIG) meeting	Guest Speaker	Dublin	10/2018
ISPOR	Poster x 2	Barcelona	11/2018
New Horizons Research Conference	Poster x 2	UCC	12/2018
College of Business and Law, and Institute for Social Science Irish Healthcare System Conference on Patient Payment	None	UCC	03/2019
SOP PhD Seminar	Oral	UCC	04/2019
Novartis Centre for Health Economics Research Seminar	Guest Speaker	Dublin	05/2019
NCPE	None	Dublin	05/2019
Cork University Business School (CUBS) Postgraduate Research Symposium	Oral	UCC	05/2019
SOP Athena Swan Research Day	Posters x 3 Oral x 1*	UCC	05/2019
International Symposium on Oncology Pharmacy Practice (ISOPP)	Poster	London	10/2019
European Health Forum Gastein (EHFG)	None	Bad Hofgastein	10/2019
EuroDURG	Posters x 2	Szeged	03/2020

* Awarded best poster/oral presentation prize at conference

8.4 Appendix IV - Chapter 2 Publication



Contents lists available at ScienceDirect

Health Policy OPEN

journal homepage: <https://www.elsevier.com/health-policy-open/>



Health policy triangle framework: Narrative review of the recent literature

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ABSTRACT

Background: Developed in the late 20th century, the health policy triangle (HPT) is a policy analysis framework used and applied ubiquitously in the literature to analyse a large number of health-related issues.

Objective: To explore and summarise the application of the HPT framework to health-related (public) policy decisions in the recent literature.

Methods: This narrative review consisted of a systematic search and summary of included articles from January 2015–January 2020. Six electronic databases were searched. Included studies were required to use the HPT framework as part of their policy analysis. Data were analysed using principles of thematic analysis.

Results: Of the 2217 studies which were screened for inclusion, the final review comprised of 54 studies, mostly qualitative in nature. Five descriptive categories of themes emerged (i) health human resources, services and systems, (ii) communicable and non-communicable diseases, (iii) physical and mental health, (iv) antenatal and postnatal care and (v) miscellaneous. Most studies were conducted in lower to upper-middle income countries.

Conclusion: This review identified that the types of health policies analysed were almost all positioned at national or international level and primarily concerned public health issues. Given its generalisable nature, future research that applies the HPT framework to smaller scale health policy decisions investigated at local and regional levels, could be beneficial.

1. Introduction

The World Health Organisation (WHO) defines health policy as ‘the decisions, plans, and actions (and inactions) undertaken to achieve specific health care goals within a society or undertaken by a set of institutions and organisations, at national, state and local level, to advance the public’s health’ [1]. Health policy informs decisions like which health technologies to develop and utilise, how to structure and fund health services, and which pharmaceuticals will be freely available [2]. Appreciating the intrinsic relationship between health policy and health, and the impact that other policies have on health, is crucial as it can help to address some of the major health problems that

exist. However, health policy decisions are not always the result of a rational process of discussion and evaluation of how a particular objective should be met. The context in which the decisions are made can often be highly political and concern the degree of public provision of healthcare and who pays for it [3]. Health policy decisions can also be conditional on the value judgements implicit in society. As a result, health policies do not always achieve their aims and implementation targets [4,5]. Consequently, health policy analysis is regularly undertaken to understand past policy failures and successes and to plan for future policy implementation [6].

Just as there are various definitions of what policy is, there too are many ideas about the analysis of health policy, and its focus [2,6]. However, what a lot of health policy analysis studies have in common, whether that be analysis of policy or analysis for policy [7], is the use of a policy framework. A myriad of policy frameworks and theories exists [8]. The burgeoning literature of health policy analysis sees novel policy frameworks being developed quite frequently with the ‘policy cube’ approach being the latest addition [8]. A recent literature review investigated the application of some of the most commonly applied frameworks [9]: the advocacy coalition framework (ACF) [10], the staged heuristic model [11], the Kingdon’s multiple stream theory [12], the punctuated equilibrium framework [13] and the institutional analysis and development framework [13]. See online supplementary data appendix 1 for brief descriptions of policy frameworks.

Abbreviations: ACP, Advocacy Coalition Framework; AIDS, Acquired Immune Deficiency Syndrome; BMCCNET, Employment and Working Conditions Knowledge Network; GP, General Practitioner/Physician; HIC, High-Income Country; HIV, Human Immunodeficiency Virus; HPT, Health Policy Triangle (Framework); HPV, Human Papillomavirus; HRH, Human Resources for Health; LIC, Low-Income Country; LMIC, Lower-Middle-Income Country; MEDS, Medical Subject Headings; NICR, National Institute for Health and Care Excellence; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SDG, Sustainable Development Goal; UHC, Universal Health Coverage; UMIC, Upper-Middle-Income Country; UN, United Nations; WHO, World Health Organisation.

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Whilst the review did mention the health policy triangle (HPT) framework as a means to help organise and think about the descriptive analysis of key variable types, and to facilitate use of said information in one of the aforementioned political sciences: the crises/models, it did not investigate its application to public health policies.

The HPT framework was designed in 1994 by Walt and Gilson for the analysis of health sector policies, although its relevance extends beyond this sector [14]. They noted that health policy research focused largely on the content of policy, neglecting actors, context and processes (Fig. 1). Content includes policy objectives, operational policies, legislation, regulations, guidelines, etc. Actors refer to influential individuals, groups and organisations. Context refers to systemic factors: social, economic, political, cultural, and other environmental conditions. Process refers to the way in which policies are initiated, developed or formulated, negotiated, communicated, implemented and evaluated [2]. The framework, which can be used retrospectively and prospectively, has influenced health policy research in many countries with diverse systems and has been used to analyse a large number of health issues [15].

In 2015, a historic new sustainable development agenda was unanimously adopted by 193 United Nations (UN) members [16]. World leaders agreed to 17 sustainable development goals (SDGs). These goals have the power to create a better world by 2030; they strive to end poverty, fight inequality and address the urgency of climate change. The SDGs call on all sectors of society to mobilise for action at a global, local and people level. Given that an estimated 405 million of the 569 million worldwide deaths were from non-communicable diseases in 2016 [17]; approximately 810 women died every day from preventable causes related to pregnancy and childbirth in 2017 [16]; an estimated 6.2 million children and adolescents under 15 years of age died mostly from preventable causes in 2018 [16]; and approximately 38 million people globally were living with HIV in 2019 [16], SDG no. 3 aims to address these issues by ensuring healthy lives and promoting wellbeing for all [16]. This goal has many sub-targets: to reduce maternal mortality; fight communicable diseases; and all preventable deaths under five years of age; promote mental health; achieve universal health coverage (UHC); increase universal access to sexual and reproductive care, family planning and education; and many more. Fortunately, these health topics are regularly examined in the health policy literature and frequently analysed with policy frameworks like the policy triangle model [18–21].

Having established preeminence in its field, the objective of this review is to explore and summarise the application of the HPT framework to health-related (public) policy decisions in the recent literature (i.e. from January 2015 (corresponding with the year that the SDGs were launched) to January 2020). By investigating the application of the HPT framework to health policies during this time period, such analysis can inform a call to strengthen future global policy growth and implementation in line with SDG no.3, and provide a basis for the development of policy analysis work. A review of past literature has previously reported on the wide-ranging use of the HPT framework to understand many policy experiences in multiple lower-middle-income country (LMIC) settings only [15]. This is the first literature review to include a compilation of health policy analysis studies using the HPT framework in both LMIC and high-income country (HIC) settings.

2. Methods

2.1 Literature search

The Medline, CINAHL Plus with Full Text, Web of Science (Coar Collective), APA PsycInfo, PubMed and Embase databases were searched for primary, original literature in English published between 1st January 2015 and 31st January 2020. No Ge filter was applied to the searches. Given the subtle differences which exist between Medline and PubMed databases, it was deemed prudent to search both.

A search strategy was developed based on the use of index and free-text terms related to (i) Health Policy Triangle OR (ii) Policy Triangle Framework

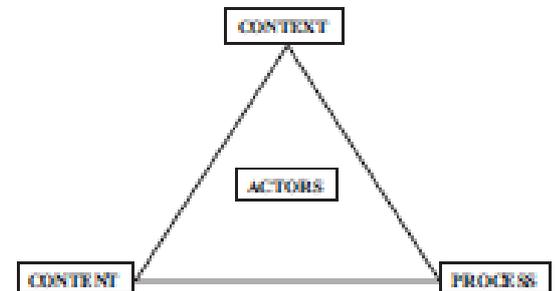


Fig. 1. Walt and Gilson policy triangle framework [14].

OR (iii) Policy Triangle Model. The lack of index terms to describe the HPT framework complicated the development of the search strategy. After much debate and perusal of the literature [9,22], a qualified medical librarian reviewed and approved a search strategy prior to undertaking the literature searches. The search strategy was pre-tested prior to use to maximise sensitivity and specificity and to optimise the difference between both. See online supplementary data appendix 2 for the complete search strategy which attempted to include medical subject headings (MeSH) and filters to ease and the use of Boolean operators.

Search results from multiple databases were transferred to a reference manager, End Note X9 [23]. Due to the broad remit of the search strategy, a 'title review' stage was conducted to remove non-pertinent studies (Fig. 2). Studies were removed in a cautious manner. An abstract review was then performed whereupon studies which clearly did not meet the inclusion criteria were excluded. The remaining studies underwent full-text review. To ensure consistency, one reviewer performed all stages of the review. Experts in academia were contacted to provide several suggestions for potentially pertinent studies. A 'snowballing' approach was used to identify additional literature through manual screening of the reference lists of the retrieved literature as well as the reference lists of such articles eligible for inclusion.

2.2 Study selection

The retrieved literature was screened for eligibility according to pre-specified inclusion and exclusion criteria (Table 1).

2.3 Study appraisal and data synthesis

The findings of each study included could not be pooled or combined as in systematic reviews or meta-analysis, and it was not deemed necessary to formally assess the study quality [24]. Indeed, due to the nature of this review, not all of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were relevant, however, insofar as was practical, the PRISMA guidelines were followed [25]. Instead, data from each study included in the review were extracted following guidance from similar studies [9,24,26,29], the National Institute for Health and Care Excellence (NICE) [27] and from the Centre for Reviews and Dissemination's guidance for undertaking reviews in healthcare [28]. Data were extracted and categorised according to country, country classification by income in 2020 [29], study design, data collection method, type and number of participants, type of analysis and health policy field (i.e. non-communicable diseases, mental health, tobacco control, etc). The health policy field of the included studies was grouped according to similarity by applying the principles of the meta-analysis [30,31]. Occasionally, ambiguity arose as to whether some of the included articles concerned health-related/public health policy issues, particularly in relation to the studies which investigated road traffic injury prevention [32] and domestic violence prevention and control [33]. In such instances, a decision of eligibility for inclusion was made after consultation with a co-author.

3. Results

3.1. Search results

From the literature searches conducted in the six databases, a total of 2217 citations were retrieved after the removal of duplicates. Based upon the title and abstract screening of the citations, 2142 articles were excluded. Another 35 articles were excluded after reading the full text. Considering the additional records identified through consultation with experts in the field and by handsearching bibliographies, a total of 54 studies were eligible for inclusion in the review. The process of study selection and reasons for exclusions are outlined in Fig. 2. Corresponding authors of all conference abstracts ($n = 9$) excluded were emailed to inquire whether a full-length manuscript of their work was published. The response rate was 100%. As of May 2020, no conference abstract had been published as a full-length manuscript.

3.2. Study characteristics

The characteristics of the 54 studies included in the review are summarized in Table 2. Forty-two of these studies describe themselves as having primarily used a qualitative study design. Data collection via various interview formats seemed to be the most common means of information

Table 1

Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
(I) Original primary research articles published in English between January 1st, 2015 and January 31st, 2020	(I) Articles not specifically related to health-related/public health policy issues
(II) Articles focused in the application of the HPT framework to health-related/public health policy issues from countries of all income levels	(II) Commentaries, conference abstracts, editorials, posters, (research/study) protocols, reports, and white papers
(III) Articles addressing all four components of the HPT framework (i.e. content of the policy; actors involved; process of policy development and implementation; context within which policy is developed)	(III) Book (chapter), thesis/dissertation and grey literature

retrieval. Eight of these studies would consider themselves to have a document analysis study design where one of the eight studies also included field work in its methodology. The remaining four studies can be described as respectively having a scoping review, mixed methods approach, literature review and theoretical analysis study design. According to country classification by income in 2020 [29], four of the included studies investigated low-income countries (LICs), 20 LMICs, 15 upper-middle income

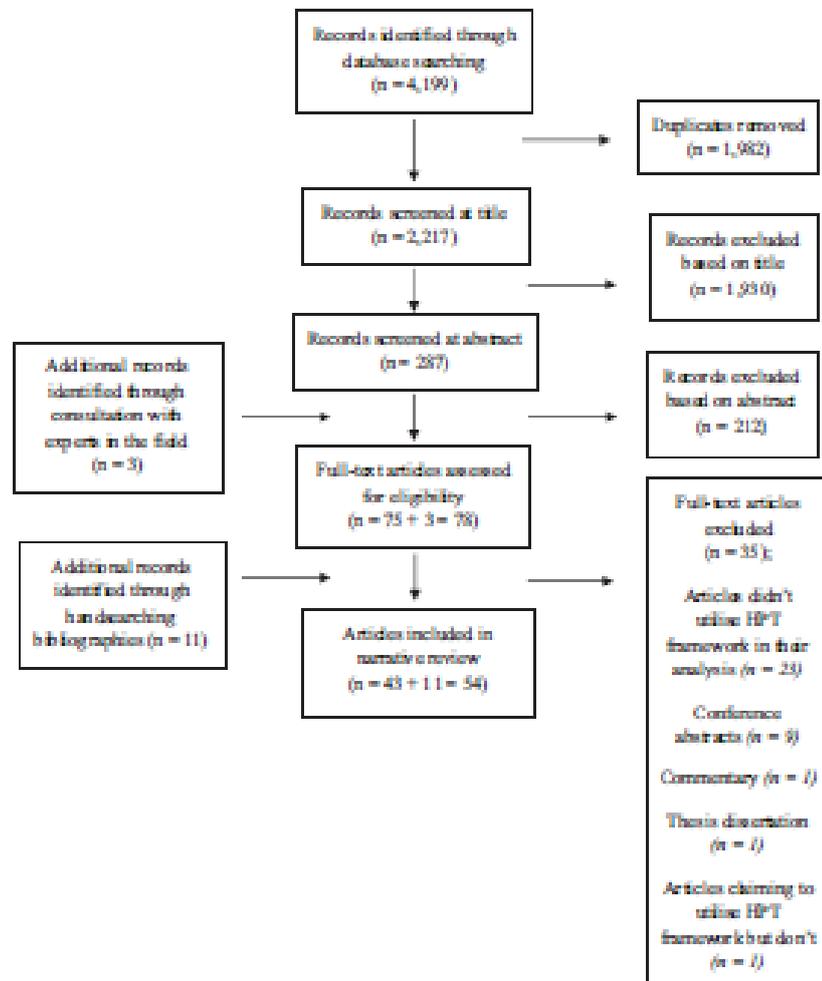


Fig. 2. Flow chart of study selection process.

Table 2
Characteristics of included studies (listed alphabetically according to first author).

Study year	Country	Country classification by Income in 2020 [39]	Study design	Data collection	Participants, (n)	Type of analysis	Health policy field
Abiona et al. [36], 2019	Nigeria	LMIC	Qualitative and scoping review	Key informant interviews, document and literature searches	Policy actors and bureaucrats, (n = 44) Documents, (n = 12)	Policy analysis	Alcohol-related policies
Abolmagedi et al. [36], 2017	Iran	LMIC	Qualitative	Semi-structured interviews and document searches	Key informants, (n = 31)	Policy analysis including stakeholder analysis	Medication safety policy to restrict look-alike medication names
Algul et al. [37], 2017	Turkey	LMIC	Qualitative and literature review	Informal interviews, document and literature searches	Key actors, (n = 7)	Retrospective policy analysis	Illegal drug policies
Almad et al. [38], 2019	Saudi Arabia and Kuwait	HIC and HIC	Qualitative	Semi-structured interviews, document searches and direct observation	Key officials, (n = 22)	Policy analysis	Herbal medicine registration and regulation
Ansari et al. [38], 2018	Iran	LMIC	Qualitative	Semi-structured interviews	Stakeholders, (n = 22)	Policy analysis	Palliative care policy making
Assan et al. [40], 2019	Ghana	LMIC	Qualitative	Semi-structured interviews	Participants, (n = 67)	Policy analysis	Challenges to achieving UHC through community-based health planning and services delivery approach
Asuni-Aghdash et al. [33], 2017	Iran	LMIC	Qualitative and literature review	Semi-structured interviews, document and literature searches	Stakeholders, (n = 42)	Policy analysis	Road traffic injury prevention
Chen et al. [41], 2019	China	LMIC	Qualitative	Semi-structured interviews and document searches	Key actors, (n = 15)	Policy analysis including stakeholder analysis	HPV vaccination programme
Doshmangir et al. [22], 2019	Iran	LMIC	Qualitative	Semi-structured interviews, document analysis and round-table discussion	Stakeholders, (n = 22) Round-table discussion (constituting of senior policy makers, n = 12)	Policy analysis (HPT incorporating the stage heuristic model)	UHC facilitation in primary healthcare
Dusumti et al. [42], 2016	Indonesia, Sudan and Tanzania	LMIC, LMIC and LIC	Field work and document analysis	Field research, document and literature searches	Direct contact with relevant ministries and agencies, (n = 5) Documents, (n = 7)	Policy analysis	Implementation of the health workforce commission announced at the third global forum on HRH
Eshiba et al. [40], 2015	Nigeria	LMIC	Qualitative and document review	In-depth interviews and document searches	Policy actors, (n = 9)	Retrospective policy analysis	Oral health policy
Fazli et al. [44], 2015	Iran	LMIC	Document analysis	Document searches	Documents, (n = 21)	Retrospective policy analysis	Diabetes prevention and control
Gao et al. [45], 2019	China	LMIC	Qualitative	Semi-structured interviews and document analysis	Key actors, (n = 3)	Retrospective policy analysis	National adolescent mental health policy
Haffan et al. [46], 2018	India, Thailand and Turkey	LMIC, LMIC and LMIC	Scoping review	Journal, article, report and book searches	Articles, (n = 26)	Comparative policy analysis	Medical tourism policy
Hansen et al. [47], 2017	Denmark	HIC	Literature review	Journal, article, newspaper and website searches	Articles, (n = 11) Newspaper (n = 14)	Prospective policy analysis (Ringden model) used in addition to HPT ^a	Implementation of out-of-pocket payments to GPs
Islam et al. [48], 2018	Bangladesh	LMIC	Qualitative	In-depth interviews and document searches	Stakeholders, (n = 42)	Policy analysis	Contracting out urban primary health care
Jamder et al. [49], 2018	Bangladesh	LMIC	Qualitative and literature review	Key informant interviews, document and literature searches	Policy elites, (n = 11)	Policy analysis including stakeholder analysis and mapping	Doctor retention in rural settings
Juma et al. [50], 2015	Kenya	LMIC	Qualitative and documents review	Semi-structured interviews and document searches	Stakeholders, (n = 19) Documents, (n = 14)	Retrospective policy analysis	Integrated community case management for childhood illness
Juma et al. [51,52], 2018	Cameroon, Kenya, Malawi, Nigeria and South Africa	Varied	Qualitative and documents review	Key informant interviews and document searches	Debate-makers, (n = 202) Documents, (n = 274)	Policy analysis ^b	Multi-sectoral action to non-communicable disease prevention policy development and process
Kalder et al. [53], 2018	South Africa	LMIC	Qualitative	Semi-structured interviews	Stakeholders, (n = 10)	Policy analysis	Regulation to limit salt intake and prevent non-communicable diseases
KNM et al. [54], 2017	Cambodia	LMIC	Qualitative and literature review	Key informant interviews, document and literature searches	Participants, (n = 29) Documents, (n = 7)	Policy analysis	Contracting of health services policy
Le et al. [55], 2019	Vietnam	LMIC	Qualitative and documents review	Key informant interviews and document searches	Policy actors, (n = 36) Focus groups, (n = 4) Documents, (n = 63)	Policy analysis	Domestic violence prevention and control
Ma et al. [56], 2015	China	LMIC	Qualitative and literature review	In-depth interviews, document and literature searches	Key actors, (n = 30) Focus groups, (n = 15) Documents, (n = 95)	Policy analysis	Task shifting of HIV/AIDS case management to community health service centres

Table 2 (continued)

Study year	Country	Country classification by income in 2020 [29]	Study design	Data collection	Participants, (n)	Type of analysis	Health policy field
Mambulu-Chikankhed et al. [56], 2018	South Africa	UMC	Qualitative and document review	In-depth interviews and document searches	Stakeholders, (n = 15) Patient records, (n = 20)	Policy analysis	Role of community health workers in malnutrition management
Mapa-Tsou et al. [57], 2018	Cameroon	LMC	Qualitative and document review	In-depth interviews and document searches	Stakeholders, (n = 20) Documents, (n = 19)	Policy analysis	Tobacco prevention and control policies
Mbachu et al. [58], 2016	Nigeria	LMC	Qualitative and document review	In-depth interviews and document searches	Key informants, (n = 10) Documents, (n = 5)	Retrospective policy analysis	Integrated maternal newborn and child health
McNamara et al. [59], 2017	Trans-Pacific countries	Varied	Document analysis	Document search(es)	Documents, (n = 1)	Prospective policy analysis (RMCONSE framework used in addition to HPT) ^a	Trans-Pacific partnership agreement and associated potentially serious health risks
Milfeldt et al. [60], 2017	Canada	HIC	Qualitative and document review	Key informant interviews and document searches	Stakeholders, (n = 20) Documents, (n = 119)	Comparative policy analysis	Team-based primary healthcare policies
Mohamed et al. [61], 2018	Kenya	LMC	Qualitative and document review	Key informant interviews and document searches	Participants, (n = 39) Documents, (n = 24)	Policy analysis	Formulation and implementation of tobacco control policies
Mohani et al. [62], 2019	Iran	UMC	Qualitative and documents review	Semi-structured interviews and document searches	Informants and policymakers, (n = 25)	Policy analysis (Kingdon model utilized in addition to HPT)	Prevention of malnutrition among children under five years of age
Mokhles et al. [63], 2018	South Africa	UMC	Document analysis	Document searches	Documents, (n = 10)	Policy analysis	Child and adolescent mental health policy
Moshiri et al. [64], 2015	Iran	UMC	Qualitative and literature review	Semi-structured interviews document and literature searches	Key participants, (n = 35)	Policy analysis (Kingdon model utilized in addition to HPT)	Formation of primary health care in rural Iran in the 1980s
Mulatu et al. [65], 2017	Zambia	LMC	Qualitative and document review	Key informant interviews and document searches	Stakeholders, (n = 8) Documents, (n = 6)	Policy analysis	Non-communicable disease policy response
Munabi-Babigumira et al. [66], 2019	Uganda	LIC	Qualitative and document review	In-depth interviews and document searches	Key informants, (n = 18)	Policy analysis	Skilled birth attendance policy implementation
Murithi et al. [67], 2018	South Africa	UMC	Qualitative and documents review	Key informant interviews and document searches	Participants, (n = 56) Focus groups, (n = 3)	Policy analysis (U's conceptual framework used in addition to HPT) ^a	Emergence of three-CP contracting-in models
Mwagomba et al. [68], 2018	Malawi	LIC	Qualitative and document review	Semi-structured interviews and document searches	Key informants, (n = 32) Documents, (n = 12)	Policy analysis	Multi-sectoral action in the development of alcohol policies
Nogueira Jr et al. [69], 2018	Brazil, Chile, Israel	UMC, HIC, LIC	Qualitative and document analysis	Non-structured interviews, observations and document searches	National team members, (n = 7)	Policy analysis ^a	Implementation of national programmes for the prevention and control of healthcare associated infections
O'Connell et al. [70], 2018	Australia, Canada, Ireland, Scotland, Wales	All HIC countries	Document analysis	Document searches	Documents, (n = 8)	Comparative Policy analysis	Frameworks to improve self-management support for chronic diseases
Odoch et al. [71], 2015	Uganda	LIC	Document analysis	Document searches	Documents, (n = 153)	Policy analysis (other framework used in addition to HPT) ^a	Male circumcision for HIV prevention policy process
Obanwadi et al. [72], 2018	France	HIC	Document and literature review	Document and literature searches	Documents, (n = 7) Articles, (n = 4)	Retrospective policy analysis	Non-implementation of HPV vaccination coverage in the pay for performance scheme
Oladipo et al. [73], 2018	Nigeria	LMC	Qualitative and document review	Key informant interviews and document searches	Stakeholders, (n = 44) Documents, (n = 18)	Policy analysis (other framework used in addition to HPT) ^a	Development and application of multi-sectoral action of tobacco control policies
Rene et al. [74], 2018	Philippines	LMC	Qualitative and literature review	Semi-structured interviews document and literature searches	Key informants, (n = 21)	Policy analysis (components of ACP and Kingdon model utilized in addition to HPT)	School food policy development and implementation
Roy et al. [75], 2019	India	LMC	Qualitative and document review	In-depth interviews and document searches	Key stakeholders, (n = 11) Documents, (n = 6)	Policy analysis including stakeholder analysis	Adolescent mental health policy
Saito et al. [76], 2015	Low	LMC	Qualitative and documents review	Key informant interviews and document searches	Policy implementers, (n = 20)	Policy analysis	National school health policy implementation

(continued on next page)

Table 2 (continued)

Study year	Country	Country classification by income in 2020 [29]	Study design	Data collection	Participants, (n)	Type of analysis	Health policy field
Shinywa et al. [77], 2019	Kenya	LMIC	Qualitative and documents review	Key informant interviews and document searches	Policy stakeholders, (n = 6) Documents, (n = 22)	Policy analysis	Translation of the UN declaration to national policies for diabetes prevention and control
Srinivasa et al. [78], 2018	India	LMIC	Document and literature review	Document and literature searches	Documents, (n = 22)	Retrospective policy analysis	Patient-oriented care in maternal and newborn health, family planning and abortion policies
Tokar et al. [79], 2019	Ukraine	LMIC	Qualitative and document review	Semi-structured interviews and document searches	Key stakeholders, (n = 14) Documents, (n = 75)	Policy analysis (other frameworks used in addition to HPT) ^a	HIV testing policies among female sex workers
Van de Paer et al. [80], 2019	Ghana	LIC	Mixed-method approach	Semi-structured interviews and quantitative data collection	Key actors, (n = 22)	Prospective policy analysis	Health workforce development and retention post-RSHP outbreak
Van de Paer et al. [81], 2017	37 countries and 27 other entities	Varied	Qualitative and literature review	Semi-structured document and literature searches	Government representatives from different countries, (n = 25)	Policy analysis	Implementation of the HSH control measures announced at the third global forum on HSH
Vos et al. [82], 2016	Netherlands	HIC	Qualitative and document analysis	Semi-structured interviews and document searches	Key stakeholders, (n = 12) Documents, (n = 64)	Policy analysis including stakeholder analysis	Improvement of perinatal mortality
Wisdom et al. [83], 2018	Cameroun, Kenya, Nigeria, Malawi, South Africa, and Togo	Varied	Qualitative and documents review	Key informant interviews and document searches	Participants, (n = 202) Documents, (n = 7)	Policy analysis ^d	Influence of the WHO framework convention on tobacco control on tobacco legislation and policies
Witter et al. [84], 2016	Cambodia, Sierra Leone, Uganda and Zimbabwe	LMIC, LIC, LIC and LMIC	Qualitative and documents review	Key informant interviews and document searches	Participants, (n = 109) Documents, (n = 270)	Comparative policy analysis including stakeholder mapping	Patterns and drivers of HSH policy-making in post-conflict and post-crisis health systems
Zhu et al. [85], 2018	China	UMIC	Qualitative and literature review	Semi-structured interviews, document and literature searches	Senior policy makers, (n = 2)	Policy analysis ^d	Progress of military-related policies
Zupanets et al. [86], 2018	Ukraine	LMIC	Theoretical analysis	Document and literature searches	Documents, (n = 7)	Policy analysis ^b	Development of theoretical approaches to pharmaceutical care improvement and health system integration

Abbreviations: ACCP - Advocacy Coalition Framework; AIDS - Acquired Immunodeficiency Syndrome; BMCD NHT - Employment and Working Conditions Knowledge Network; GP - General Practitioner/Physician; HIC - High-Income Country; HIV - Human Immunodeficiency Virus; HPT - Health Policy Triangle (Framework); HPT - Human Papillomavirus; HRH - Human Resources for Health; LIC - Low-Income Country; LMIC - Lower-Middle-Income Country; UNIC - Universal Health Coverage; UMIC - Upper-Middle-Income Country; UN - United Nations; WHO - World Health Organization; ? - Not specifically mentioned in stated text.

^a Hama et al. [47], 2017 - Content and process factors omitted in HPT analysis but justified elsewhere in manuscript.

^b Juma et al. [51,52], 2018 - Juma et al. have published two study papers on a related topic from the same project using the same retrieved data sources. Thus, given the similarity, one data entry was deemed sufficient to encompass these two related study papers.

^c McNamara et al. [59], 2017 - A framework by the BMCD NHT of the WHO Commission on the Social Determinants of Health that comprehensively outlines pathways to health via labour markets [87].

^d Mwanthi et al. [87], 2018 - A conceptual framework by Liu et al. [88] on the impact of 'contracting-out' on health system performance.

^e Noguera-Jr et al. [89], 2018 - Actor factor omitted in HPT analysis but justified elsewhere in manuscript.

^f Odach et al. [71], 2015 - Bepoke framework is used that was conceived from Walt and Gilson's concepts for analyzing the inter-relationships between actors, process, and context [14]. Odach et al. also cited Kingdon's multiple stream theory model [12], Foucault's concept of power [90] and the Glanville et al. [91] concept of position mapping of actors, in their bepoke framework.

^g O'Keefe et al. [73], 2018 - Interview guides were informed by the Walt and Gilson policy analysis framework [14] and the McQueen analytical framework for interactional action [92].

^h Tokar et al. [79], 2019 - A framework analysis initially developed by Goffman et al. [80] and adapted by Colwell et al. [94] was used in order to examine how the HIV/AIDS programme was conceptualised.

ⁱ Wisdom et al. [83], 2018 - Wisdom et al. use the same key informant interviews data source that was utilized by Juma et al. [51,52].

^j Zhu et al. [85], 2018 - Authors purport to use a policy triangle framework proposed by Hawkes et al. [93]. Upon further inspection and email contact with Hawkes, the framework used was in fact the HPT model originally proposed by Walt and Gilson [14] in which study was included in the review. It is assumed that the authors accidentally mislabeled the policy triangle framework in their study.

^k Zupanets et al. [86], 2018 - It is unclear which genre of study design best describes this article. For the purposes of this review, its study design was classified as a 'theoretical analysis'.

countries (UMICs), and six HICs. Eight studies were classed as 'varied' due to multiple countries of different classifications of income being simultaneously examined. All the included studies can be described as some variant of policy analysis. Certain articles highlighted whether the policy analysis was retrospective, prospective or comparative in nature; approximately 20% of the studies incorporated additional conceptual frameworks. Such additional details are outlined in the 'Type of analysis' column in

Table 2. Six studies conducted a supplementary stakeholder analysis/mapping [3-4].

3.3 Study findings

From the content analysis approach to the health policy fields of the included studies, five broad descriptive conceptualised themes were identified

demonstrating how the HPT framework was applied to health-related (public) policy decisions in the recent literature: (i) health human resources, services and systems, (ii) communicable and non-communicable diseases, (iii) physical and mental health, (iv) antenatal and postnatal care and (v) miscellaneous. Unsurprisingly, many of the health policy fields explored in the included studies aimed to address sub-targets of SDG no. 3 [16].

3.3.1. Health human resources, services and systems

The implementation of the human resources for health (HRH) commitment announced at the third global forum on HRH [96], with particular attention given to health workforce commitments, were analysed by two separate studies for different countries [42,81]. Another study by Witter et al. focused on the patterns and drivers of HRH policy-making in post-conflict and post-crisis health systems: namely those of Cambodia, Sierra Leone Uganda and Zimbabwe, all lower to lower middle-income countries. Similarly, Van de Paas et al. conducted a policy analysis study which sought to inform capacity development that aimed to strengthen public health systems, and health workforce development and retention, in a post-Ebola LIC setting [80]. Indeed, health workforce retention policy analysis was also carried out by Joarder et al. where retaining doctors in rural areas of Bangladesh was a challenge [49].

Two studies looked at potential issues and policies surrounding UHC facilitation in the primary healthcare setting [22,40]. The somewhat related concept of contracting health services arose in these studies where it was explored in relation to contracting for public healthcare delivery in rural Cambodia [54], contracting-out urban primary healthcare in Bangladesh [48], and the emergence of three general practitioners/physician (GP) contracting-in models in South Africa [67].

At primary and community healthcare level, a variety of policy analysis studies scrutinised topics like the formation of primary healthcare in rural Iran in the 1980s [64], contextual factors and actors that influenced policies on user-based primary healthcare in Canada [60], the potential implementation of out-of-pocket payments to GPs in Denmark [47], and policy resistance surrounding integrated community case management for childhood illness in Kenya [50].

There were three policy analysis studies which focused on medicines and pharmaceutical safety within the health system. Abolhasani et al. reviewed medication safety policy that saw the establishment of the drug naming committee to restrict look-alike medication names [36]. Akmal et al. investigated herbal medicine registration systems policy [38] while Zupanski et al. sought to formalise theoretical approaches to the improvement of pharmaceutical care and health system integration [86].

3.3.2. Communicable and non-communicable diseases

The policy response to non-communicable diseases by the Ministry of Health in Zambia was explored by Mukamu et al. [65], where similarly, Juma et al. investigated non-communicable disease prevention policy development and processes, and how multi-sectoral action is involved [51,52]. Kallor et al. analysed policy which used regulation to limit salt intake and prevent non-communicable diseases [83]. O'Connell et al. compared frameworks from different countries that aimed to improve self-management support for chronic (non-communicable) diseases [70]. Two studies focused on diabetes, one of the leading non-communicable diseases worldwide, where prevention and control policies for the disease state were reviewed [44,77].

Communicable disease policy analysis studies concentrated on two main viruses: human immunodeficiency virus (HIV) and human papillomavirus (HPV). Analyses in relation to HIV looked at the feasibility of implementation and non-implementation of a HPV vaccination programme in upper-middle to high income countries [41,72]. HIV-related studies varied from policies like task shifting of HIV/AIDS case management to community health service centres [58], and male circumcision for HIV prevention [71], to HIV testing policies among female sex workers [79]. Noguera-Jr et al. investigated the implementation of national programmes for the prevention and control of healthcare associated infections in three upper-middle to high income countries [69].

3.3.3. Physical and mental health

Alcohol consumption, illegal drug ingestion, nutritional habits and tobacco inhalation are all potential determinants of the quality of physical health status. Four studies investigated varying factors surrounding tobacco control policies [57,61,73,83]. Two studies examined alcohol-related policies [35,68] where one study scrutinised illegal distilling policies [37]. Three studies explored nutrition: two focusing on malnutrition management and prevention in LMICs [56,62] and one reviewing school food policy development and implementation in the Philippines [74]. Interestingly, all three mental health policy analysis studies included in this review focused on the topic of child, and mostly, adolescent mental health policy [45,63,75].

3.3.4. Antenatal and postnatal care

Policy analysis studies regarding pregnancy and mother and child wellbeing featured strongly. Zhu et al. outlined the progress of midwifery-related policies in contemporary and modern China [85] while Mumbi-Sabigumira et al. analysed the strategies implemented and bottlenecks experienced as Uganda's skilled birth attendance policy was launched [56]. Other studies looked at the various factors which promoted or impeded agenda setting and the formulation of policy regarding perinatal healthcare reform [82], person-centred care in maternal and newborn health, family planning and abortion policies [78], and the integrated maternal newborn and child health strategy [58].

3.3.5. Miscellaneous

There were some other policy analysis studies that can be treated as standalone articles within the context of this review: palliative care system design [39]; national law on domestic violence prevention and control within the health system [33]; oral health policy development [43]; road traffic injury prevention [32]; national school health policy implementation [76]; and medical tourism policy [46]. Interestingly, given that the impact of the Trans-Pacific partnership agreement on employment and working conditions is a major point of contention in broader public debates worldwide [97], one prospective policy analysis study examined the potential health impacts of the Trans-Pacific partnership agreement [98] by investigating labour market pathways [59].

4. Discussion

From the findings of this review, the most common method of data collection was by means of some form of interview with participants involved in the relevant policy area. The same finding was found in a similar review [15]. Talking to actors can provide rich information for policy analysis. These collection methods may be the only way to gather valid information on the political interests and resources of relevant actors and to gather historical and contextual information. Indeed, interviews are generally more useful in eliciting information of a more sensitive nature where the goal of the interview is to obtain useful and valid data on stakeholders' perceptions of a given policy issue [2]. However, interview data can be ambiguous in the sense that what interviewees say and the manner in which they say it, may contrast what one actually thinks or does. Many of the studies included in this review overcame this potential limitation by triangulating the responses with additional responses from other informants, or with data collected via alternative channels, particularly documentary sources.

Many different types of policy fields were unashed throughout the data extraction process. Quite a lot of the studies reviewed targeted health policies at national level whether that policy be UHC implementation, infectious disease vaccination programmes, or malnutrition management. Some studies conducted policy analysis at international level investigating issues such as the health impact of the Trans-Pacific partnership agreement, and the implementation of the HRH commitments announced at the third global forum on HRH that involved over fifty countries. Cross-country comparative policy analysis was also common and examined topics like medical tourism, factors of HRH policy-making in post-crisis health systems, and frameworks to improve self-management support for chronic diseases. Indeed, health policy fields explored within the descriptive categorised theme 'miscellaneous' demonstrated

how wide-ranging the applicability of the HPT framework is to a variety of health-related (public) policy decisions. None of the included published literature explored policy analysis of local or regional health-related policy decisions using the HPT framework. Given its generalisable nature, further and perhaps more novel uses of the descriptive policy triangle model could be trialled in a diverse range of health policy decisions made at local and regional level.

Of the policy analysis study countries reviewed, approximately 40% were classified as LMIC settings. In recent years, such work has been incorporated into a analysis of LMIC public sector reform experiences [15] thus possibly explaining this relatively high percentage. In addition, a reader recently published by WHO to encourage and deepen health policy analysis work in LMIC settings, which considers how to use health policy analysis prospectively to support health policy change, could explain this high percentage [99]. Interestingly, notwithstanding that work conducted within the field of policy analysis is fairly well-established in the United States and Europe [100,101], only a proportionately 1.2% of the policy analysis studies yielded from this review were conducted in HIC settings. This finding is open to many interpretations with one crude deduction being that perhaps policy analysis is currently more common in LMIC settings than in HIC settings. Another possibility is that commissioned policy analysis studies in HIC settings are seldom published in peer-reviewed academic journals. Also, it may be the case that LMIC settings rely on external academics to carry out and publish their health policy analysis studies as a recently published evidence assessment reports that LMICs often have an incomplete and fragmented policy framework for research [102]. Further research is required.

All the included studies in this review can be described as some variant of policy analysis where certain articles specifically stated whether the policy analysis was retrospective, prospective or comparative in nature. In fact, the vast majority of studies can be categorised as analysis of policy rather than for policy [7]. Most of the studies still seek to assist future policy-making but are largely descriptive in nature, limiting understanding of policy change processes. Similar findings are found in the literature [15].

The comparative policy analysis studies included often involved more than one country with exception of the analysis by Misfeldt et al. who explored the context and factors shaping team-based primary healthcare policies in three Canadian provinces [60]. Although such comparative studies may introduce further challenges (such as working across multiple languages and cultures, and securing additional funding), the comparisons between similar (and different) country contexts can help disentangle generalisable effects from country context-specific effects in policy adaptation, evolution and implementation [6].

Six studies conducted a supplementary stakeholder analysis/mapping. Stakeholder analysis can be used to help understand about relevant actors, their intentions, inter-relationships, agendas, interests, and the influence or resources they have brought or could bring on decision-making processes during policy development [103]. The use of stakeholder analysis in this review was complemented by other policy analysis approaches as is corroborated by the literature [34].

Interestingly, approximately 20% of the studies in this review applied an additional analytical/theoretical framework. McNamara et al. used a framework by the Employment and Working Conditions Knowledge Network (EMCONET) of the WHO's Commission on the Social Determinants of Health [90] which comprehensively outlines pathways to health via labour markets [87]. Misfeldt et al. applied a conceptual framework by Liu et al. on the impact of contracting-out on health system performance [87,88]. Oloch et al. decided to implement many bespoke frameworks [71] that were co-created from Walt and Gilson's concepts for analysing the interrelationships between actors, process, and context [14] as well as citing the Kingdon's multiple streams theory model [12], Foucault's concept of power [90] and the Glasman et al. concept of position mapping of actors [91]. Olatope et al. utilised the McQueen analytical framework for inter-sectoral action [73,92] while Tokar et al. incorporated a framework analysis that was initially developed by Goffman et al. and subsequently adapted by Caldwell et al. in order to examine how the HIV/AIDS programme in question was conceptualised [79,93,94]. Given that there is a paucity of theoretical and conceptual

approaches to analysis of the processes of health policy in LMIC settings [5,104], the need to use multiple bespoke frameworks in the aforementioned recent policy analyses may be a plausible finding. In addition, other research has shown that the Walt and Gilson triangle model 'needs to be operationalised and transformed in practice which may suggest that it is not fit for purpose in its primitive state [105]. This could explain why a variety of frameworks are applied alongside the HPT model in these studies.

Other studies applied the Kingdon model in addition to the HPT framework [47,62,64] whilst Reeve et al. used components of the ACF, Kingdon model and HPT framework [74]. The policy triangle model is often regarded as being descriptive in nature [9,13] thus implementation with additional frameworks such as the ACF and Kingdon model can enrich the analysis by making it more explanatory [9]. Doshmangee et al. used a tailored version of the HPT framework incorporating the stages heuristic model to guide data analysis [22]. Like the policy triangle model, the stages heuristic are often characterised as being descriptive in nature [9], thus the aforementioned study provided a highly descriptive policy analysis of UHC facilitation in the primary healthcare setting in Iran. Unsurprisingly, no single policy framework offers a fully comprehensive description or understanding of the policy process as each model answers somewhat different questions [104,106]. Existing policy frameworks have complementary strengths since policy dynamics are driven by a multiplicity of causal paths [107]. Thus, multiple frameworks can be applied as 'tools' in order to assess and plan action. However, it is important to discern which framework may be better suited to particular scenarios and policy issues [106].

Some of the 23 articles (see Fig. 2) that were excluded from this review for not utilising the policy triangle model used other bespoke and well-known health policy frameworks, with the Kingdon's multiple streams theory being the most common [12]. As previously mentioned, a 'crossfitting' approach was used to identify additional literature through manual screening of the reference lists of the reviewed literature as well as the reference lists of such articles eligible for inclusion. Eleven additional studies were identified from this strategy (Fig. 2) meaning many more were excluded for not meeting the inclusion criteria (Table 1). Such studies were too many to document. However, two articles identified from this process appeared to be quite misleading and thus noteworthy. Onwujekwe et al. described a conceptual model that they used in their policy analysis which was almost identical to the HPT framework [108]. However, as the authors didn't characterise or reference their framework to the policy triangle model or to the work of Walt and Gilson, it was omitted from the review. Similarly, Doshmangee et al. portrayed their results in such a way that correlated to the four components of the HPT framework [109]. While the authors did mention the policy triangle framework as a talking point in their discussion section, they failed to explicitly reference it in their methodology and results paragraphs. This led to the exclusion of their study from this review. It is not known why these studies didn't appropriately reference the utilisation of the HPT framework when its application was apparent. It is possible that more policy analysis studies which exist in the recent literature could be presented in a similarly ambiguous manner.

5. Limitations

The included articles were mostly qualitative in nature albeit other study designs were also utilised. Limitations inherent to such study designs may pose a bias in the quality of the included articles. Grey literature including reports may have provided important sources of information regarding the application of the HPT framework to health-related (public) policy decisions. However, given the difficulty associated with designing internet search strategies, the heterogeneous nature of grey literature documents and the additional time required, it was excluded from the review [110]. It was decided to only include primary English-language published literature on this topic from January 2015 to January 2020. It is recommended that additional reviews of other language literature be conducted in association with a wider time frame. This review does not claim to be a fully comprehensive summary of all policy analysis studies which utilised the HPT framework between 2015 and 2020. Further consultation with

additional experts, citation searching methods, and handsearching of key journals may produce more relevant articles for inclusion. However, given that the majority of studies analysed in this review are qualitative in nature, it can be argued that it is not necessary to locate every available study for such purposes [31, 111]. In addition, it is known that some of the doctoral theses and unpublished material in the field are already represented within the published literature included here. Sometimes, the components of the HPT framework i.e. actors, content, context, process are described as such in the literatures without exclusively referring to the HPT framework itself. Thus, these studies would not have been detected using the search strategy chosen for this review (online appendix 2). Finally, when compared to other research designs (e.g. systematic reviews), narrative reviews of the literature are more susceptible to bias e.g. the included articles were not evaluated for their quality [112].

6. Conclusion

This narrative review of the recent literature sought, retrieved and summarised the application of the HPT framework to health-related (public) policy decisions. Based on the findings of the review, it appears that the use of this framework appears to be ubiquitous in the health policy literature where many use authors supplement with a different health policy frameworks to further enhance their analysis. Notwithstanding a previous debate which disputes that there is a dearth of theoretical and conceptual approaches to analysis of the processes of health policy in low and middle-income countries [6, 104], this review demonstrates that the shortage of health policy analysis studies now appears to come from high-income countries. The finding suggests the need for additional health policy analyses to be conducted in such settings, or if this is already happening, the demand to publish more. In relation to the types of health policies being scrutinised, almost all were positioned at national or international level and primarily concerned public health issues. However, given its universal presence in the literature, and its unique adaptability and generalisability to many varied health policy topics, future research applying the HPT framework to smaller scale health policy decisions being investigated at local and regional levels, could be beneficial.

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Ethical approval

Ethical approval was not required.

Author contributions

Gary L. O'Brien (GLOB), Sarah-Jo Sinnott (SJS), Stephen Byrne (SB), Valerie Walsh (VW), and Mark Mulcahy (MM): GLOB was responsible for protocol design, study selection, data extraction, drafting of the manuscript and approval of the final manuscript. GLOB conceived the study idea. GLOB, SJS and SB decided on the database selection. GLOB carried out data collection. GLOB analysed and interpreted the data. GLOB wrote the final manuscript; SJS, MM, VW and SB revised the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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Online supplementary data

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8.5 Appendix V - Chapter 2 Framework descriptions

Brief Description of Policy Frameworks	
Name	Description
Advocacy Coalition Framework	The advocacy coalition framework was designed as an alternative to the stages heuristic; it intentionally avoids a linear description of the policy process (38). It addresses highly challenging issues in which there are substantial goal conflicts, important technical disputes and multiple actors from several levels of Government (40). The advocacy coalition framework examines the interaction within a policy subsystem of a small number of advocacy coalitions composed of actors from different institutions sharing similar policy beliefs (40). The advocacy coalition framework describes three tiers of beliefs: (i) deep core beliefs, (ii) policy core beliefs, (iii) secondary beliefs.
Institutional Analysis and Development Framework	The institutional analysis and development framework provides a language, and way of thinking about the means in which different institutions foster collective action. It highlights key insights on institutional, technical, and participatory aspects of collective interventions, or the commons problem, and their resulting effects (43). At the framework's core is the ' <i>action arena</i> '. The action arena is composed of an action situation and actors and is used as the unit of analysis and investigation (44). The action situation refers to a social space where the actors interact, solve the commons problem, and exchange goods and services; the actors are those who participate in the situation (40). A major advantage of the framework is bringing an institutional perspective to policy analysis, which doesn't appear to be as present in other frameworks.
Kingdon's Multiple Streams Theory	Kingdon's multiple streams theory within the policy process focuses on the role of policy ' <i>entrepreneurs</i> ' inside and outside Government who take advantage of agenda setting opportunities ' <i>policy windows</i> ' and move items onto the Government's formal

Brief Description of Policy Frameworks	
Name	Description
	agenda (30). The model postulates that policy choices are made when the three streams (problem stream, policy stream and politics stream) intersect at pivotal time points ' <i>policy windows</i> ' where opportunities can occur spontaneously (39). When a policy window opens, the policy entrepreneur must immediately seize the opportunity to initiate action.
Policy Cube	The non-communicable disease policy cube, developed as part of the PA4NCDs project, brings together three axes to assess the strength of a policy framework to combat diet-related non-communicable diseases: comprehensiveness, effectiveness and equity. The fuller the cube, the more robust the policy framework for the prevention and control of non-communicable diseases (36).
Punctuated Equilibrium Model	Punctuated equilibrium model theorises that the policymaking process is characterised by periods of stability with minimal or incremental policy change, disrupted by bursts of rapid transformation (31). The concept was initially developed in paleontology to explain sudden bursts of change in the fossil record scattered among longer-term minor changes (41). Central to the theory are the concepts of the ' <i>policy image</i> ' and the ' <i>policy venue</i> '. The model has been used to explain the tendency for policy inactivity and sudden change in health policy issues like drug abuse and pesticide control in the USA (42).
Stages Heuristic	The stages heuristic is the ' <i>idealistic</i> ' to the policy process (37). It divides the policy process into a series of five stages: (i) agenda setting, (ii) policy formulation, (iii) policy adoption, (iv) policy implementation, and (v) policy assessment. This model has been widely criticised given that its linear, systematic approach to solving policy problems is rarely found. Nonetheless, it is helpful to think of policymaking occurring in these different stages (30).

8.6 Appendix VI - Chapter 2 Search strategy

Search Terms and Strategy Devised upon Consultation with Medical Librarian:

Search Terms:

Health Policy Triangle

OR

Policy Triangle Framework

OR

Policy Triangle Model

i.e.

(Health AND Policy AND Triangle)

OR

(Policy AND Triangle AND (Model or Framework))

Search Strategy Conducted in early February 2020 (Search Restrictions: English Language only, Time period 1st January 2015 – 31st January 2020)

(A) The following is the search strategy used for Medline, CINAHL Plus with Full Text, APA PsycInfo in the EBSCO database:

1 (Health.tw AND Policy.tw AND Triangle.tw)

OR

2 (Policy.tw AND Triangle.tw AND (Model or Framework).tw)

154 for APA PsycINFO, 947 for CINAHL, 762 for Medline

(B) The following is the search strategy used for Pubmed:

1 (Health AND Policy AND Triangle) All Fields

OR

2 (Policy AND Triangle AND (Model or Framework)) All Fields

599 for Pubmed

(((((Health) AND Policy) AND Triangle AND ("2015/01/01"[PDat] : "2020/01/31"[PDat]))) OR
(((Policy) AND Triangle) AND Framework AND ("2015/01/01"[PDat] : "2020/01/31"[PDat])))
OR (((Policy) AND Triangle) AND Model AND ("2015/01/01"[PDat] : "2020/01/31"[PDat])))

(C) The following is the search strategy used for EMBASE:

1 (Health AND Policy AND Triangle) All Fields

OR

2 (Policy AND Triangle AND (Model or Framework)) All Fields

559 for EMBASE

#1 OR #2 OR #3

#3

('policy'/exp OR policy) AND triangle AND ('model'/exp OR model) AND [english]/lim AND [embase]/lim AND [1-1-2015]/sd NOT [1-2-2020]/sd

162*

#2

('policy'/exp OR policy) AND triangle AND ('framework'/exp OR framework) AND [english]/lim AND [embase]/lim AND [1-1-2015]/sd NOT [1-2-2020]/sd

63*

#1

('health'/exp OR health) AND ('policy'/exp OR policy) AND triangle AND [english]/lim AND [embase]/lim AND [1-1-2015]/sd NOT [1-2-2020]/sd

(D) The following is the search strategy used for Web of Science:

1 ALL=(Health AND Policy AND Triangle) ALL = All Fields

OR

2 ALL=(Policy AND Triangle AND Model)

OR

3 ALL=(Policy AND Triangle AND Framework)

1 OR 2 OR 3 = 1,178 for Web of Science

6

1,178

#5 OR #4 OR #3

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=2015-2020

5

515

(ALL=(Policy AND Triangle AND Model)) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=2015-2020

4

231

(ALL=(Policy AND Triangle AND Framework)) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=2015-2020

3

873

(ALL=(Health AND Policy AND Triangle)) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=2015-2020manual

8.7 Appendix VII - Chapter 3 Publication

Biosimilar infliximab introduction into the gastroenterology care pathway in a large acute Irish teaching hospital: a story behind the evidence

Gary L O'Brien¹, BPharm, MPharm; Donal Carro²; Mark Mulcahy³; Valerie Walshe⁴; Professor Garry Courtney²; Professor Stephen Byrne¹

Introduction/Background and aim: Biosimilar medicines are not considered exact replicas of originator biological medicines. As a result, prescribers can be hesitant to introduce such medicines into the clinical setting until evidence surfaces confirming their safety and effectiveness. In Ireland, a national biosimilar medicines policy is currently in development but the decision to prescribe biosimilar medicines remains at the discretion of the physician. The aim of this descriptive review is to tell the story of the evidence used by a large acute Irish teaching hospital to introduce biosimilar infliximab CT-P13 for the treatment of inflammatory bowel disease (IBD) in a safe and timely manner into routine care.

Methods: To explore the evidence supporting the effective introduction of biosimilar infliximab in a large acute Irish teaching hospital, a literature review was conducted. Evidence consisted of published studies, reviews, reports, position statements, articles, clinical guidelines and recommendations from national bodies, regulatory authorities and professional organizations. All evidence was published in English.

Results and conclusion: In September 2014, the accumulated evidence base provided physicians with reassurance to prescribe biosimilar infliximab CT-P13 for new patients suffering from IBD in this large acute Irish teaching hospital. In September 2016, as the evidence base grew, physicians began to safely and confidently switch patients from the originator infliximab product to the biosimilar product.

Conclusion: There was a significant time lag between regulatory approval and clinical acceptance given that the European Medicines Agency (EMA) had granted market authorization for biosimilar infliximab CT-P13 three years prior to the initiation of this hospital's switching process. Although conservative in their execution, the authors conclude that with the existential concern and uncertainty still surrounding biosimilar medicines, a distinct and individualized approach for biosimilar medicine implementation is required. It is hoped that the Irish biosimilar medicines policy will improve upon biosimilar medicine clinical acceptance once published.

Keywords: Biologicals, evidence-based, inflammatory bowel disease, switching, secondary care

Introduction

In 2014, six of the top 10 blockbuster medicines were monoclonal antibodies [1]. In recent times, small molecule chemical entity (SMCE) blockbuster drugs like Viagra[®] and Lipitor[®], have been superseded by blockbuster biologicals such as Humira[®] and Enbrel[®], demonstrating the newly acquired prominence of biological medicines [2, 3]. However, these large complex proteins (comprised of or derived from living cells or organisms) are more complicated than traditional SMCEs due to their unique manufacturing process [4]. Unlike generic drugs of SMCEs, biosimilar medicinal products (biosimilars) which aim to replicate originator biological products, have given rise to concerns related to their pharmaceutical quality, safety (especially immunogenicity) and efficacy (particularly in extrapolated indications) [5, 6]. This can create confusion around the practice of interchangeability which is not as lucid for biosimilars as it is for generic drugs of SMCEs [7].

Substitution, switching and interchangeability are terms often used when discussing biosimilars. Pharmacists can substitute generic drugs of SMCEs in Ireland and the UK on the proviso these medicines are deemed interchangeable [7–9]. The European Medicines Agency (EMA) defines substitution as 'use

practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the prescriber' whilst interchangeability refers to 'the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect' [10]. However, pharmacist substitution of biosimilars is not currently permitted in most countries [4, 11], although pharmacists practising in Australia can substitute some biological medicines [12]. In the majority of cases, it appears that pharmacists are bound by legislative constraints at the point of dispensing [13]. As a result, physicians are the key stakeholders to switch patients to and from different brands of the same or similar biological medicines, where switching is defined as 'when the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent' [10].

There is no longer a dearth of evidence when it comes to the science and interchangeability status of biosimilar medicines. However, knowing when it is most appropriate and timely to implement these medicines into routine clinical practice can be difficult. In a large acute Irish teaching hospital, biosimilar infliximab CT-P13 was introduced in place of originator brand infliximab (Remicade[®]), to treat inflammatory bowel disease

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REVIEW ARTICLE

(IBD). As well as Crohn's disease (CD) and ulcerative colitis (UC), Remicade® is licensed to treat a range of other autoimmune diseases, such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and psoriasis [14]. In the absence of a national Irish biosimilar medicines policy and with perceived uncertainty surrounding biosimilar medicines, this descriptive review adds to the literature by illustrating the independent systematic evidence base behind the decision-making process to introduce biosimilar infliximab CT-P13 into secondary care treatment of IBD.

Methods

In June 2013, biosimilar infliximab was licensed by EMA [15]. The agency's committee for medicinal products for human use (CHMP) recommended the granting of marketing authorizations for the first two monoclonal antibody biosimilars, Remsima® and Inflectra®, both of which contain the same known active substance infliximab CT-P13. The decision to provide marketing authorization for both these infliximab biosimilar medicines was based on the same documentation. Their application dossiers demonstrated parallel similarity to the biological medicine Remicade®, which has been authorized in the European Union (EU) since 1999 [15]. Remsima® and Inflectra® are recommended for authorization in the same indications as Remicade®.

A few weeks after biosimilar infliximab CT-P13 was licensed, the European Crohn's and Colitis Organisation (ECCO) released a position statement. In it, they articulated that post-marketing pharmacovigilance and unequivocal identification of infliximab CT-P13 as a biosimilar was in place. However, their overall stance on the issue was that the use of most biosimilars in patients with IBD should require testing in this particular patient population with comparison to the appropriate innovator product (Remicade®) before approval [16]. ECCO also considered the benefits of wider access with appropriate use of biological therapy in IBD and potential direct cost savings important but its primary concern was that rigorous testing was necessary in patients with IBD to ensure that appropriate efficacy and safety standards were met. The organization was of the opinion that final clinical decisions should always be made on an individual basis, taking into account both the circumstances of the individual patient and the prescribing physician. ECCO defied the practice of extrapolation for biosimilar infliximab at this time. In addition to stance taken by ECCO, several national physician societies initially questioned the marketing authorizations of biosimilars, including the extrapolation to IBD. Retrospectively, it became obvious that there was a lack of understanding of the biosimilar development concept [17].

Contrary to the guidance from ECCO, the chief pharmacist and consultant gastroenterologist of a large acute Irish teaching hospital decided to introduce biosimilar infliximab CT-P13 for use in new patients in September 2014. Both parties had been documenting the evidence trail since the licensing of this biosimilar in June 2013 and believed there was enough accumulated evidence from various sources to support their decision [15, 16]. This information was relayed to all prescribing physicians during an internal staff meeting where the chief pharmacist and consultant gastroenterologist explained the science behind their evidence-based decision. All physicians accepted this decision

and agreed to prescribe biosimilar infliximab CT-P13 for new patients. Physicians agreed to report any adverse drug reactions (ADRs) to the Health Products Regulatory Authority (HPRA) in Ireland and to EMA. Hospital budget coordinators were pleased given that the biosimilar product was cheaper than the originator brand. With verbal reassurance to patients on the safety and efficacy at the point of prescribing, physicians faced no opposition from new patients.

Although this new prescribing practice could have been deemed hasty, the British Society of Gastroenterology (BSG) released a position statement with updated guidance two months later justifying the introduction of biosimilar infliximab CT-P13 in the clinical setting. The BSG recommended that infliximab should be prescribed by brand name [19]. This prescribing practice contradicts the trend for SMCE medicines where prescribing generically is encouraged [7]. This statement also proposed the use of a prospective registry of all biological use in IBD patients to capture safety data and side effects. For patients already on therapy, it was recommended to avoid switching from the originator product to the biosimilar, or vice versa, at least until safety data was made available [19].

During the summer of 2015, the National Institute for Health and Care Excellence (NICE) remarked positively on the topic of biosimilar prescribing. Their report concluded that EMA was content that the pharmacokinetics, efficacy, safety and immunogenicity profiles of biosimilars were similar to those of the originator product and concluded that the recommendations for infliximab could apply both to the originator product and its biosimilars [20]. In addition, the HPRA released a guide to biosimilars for healthcare professionals (HCPs) and patients in December 2015. This guide discussed the concept of extrapolation in the context of biosimilars where a clinical study is carried out in one of the approved indications of the biological medicine and the efficacy data are then extrapolated to all authorized indications [11]. As stated in this guide, extrapolation is not unique to the authorization of biosimilars; a similar approach may also be used to deal with post-authorization changes for reference biological medicines.

In February 2016, both NICE and the BSG updated their previous guidance on this subject. NICE reinforced that all HCPs should ensure biological medicines, including biosimilar medicines, are prescribed by brand name so that products cannot be automatically substituted at the point of dispensing. The choice of whether a patient receives a biosimilar or originator biological medicine should rest with the clinician in consultation with the patient [4]. The BSG however decided to go one-step further, releasing a position statement on infliximab brand switching. Their guidance stated that there was sufficient evidence to recommend that patients who were in stable clinical response or remission on Remicade® therapy can be switched on the same dose and dose interval to biosimilar infliximab CT-P13. This switch should be carried out after discussion with individual patients with an accompanying explanation for switching (which is usually on the grounds of benefit to the overall service by reduction in costs of the drug and its administration) [19]. Despite the position statement from the BSG, this large acute Irish teaching hospital judged that it was premature

to switch all of its patients from Remicade® to biosimilar infliximab CT-P13.

Two months later, a review entitled 'Switching to biosimilar infliximab (CT-P13): evidence of clinical safety, effectiveness and impact on public health' published in *Biologics Journal* concluded that whilst prudent switching practices should be employed, growing safety experience accumulated thus far with infliximab CT-P13 and other biosimilars was favourable and did not raise any specific concerns [21]. Similar evidence that was in favour of switching had also started to surface [19, 22]. In June 2016, ScienceDaily published a research article on their website entitled 'Biosimilar switching not suitable for all patients' [23]. At first, it appeared to the consultant gastroenterologist and chief pharmacist that this article, based on a study conducted in Spain [24], would counteract previous evidence in favour of switching. However, when examined closely, the results of the study showed that when anti-drug antibodies develop in response to Remicade®, these antibodies also cross-react with biosimilar infliximab CT-P13 as both biologicals share structural properties, including antigenic epitopes. These findings suggested that antibody-positive patients being treated with Remicade® should not be switched to biosimilar infliximab CT-P13 since these antibodies would also interact with the biosimilar and potentially lead to a loss of response. Despite its misleading title, the results of this research article actually emphasized the similarities between the originator and biosimilar brands of infliximab and reinforced the science behind the safety of switching. In fact, it should be reinforced that anti-drug antibodies prevent a switch only if the exposure or clinical effect of the reference product is fading.

July 2016 saw the European Commission (EC) release guidance stating that biosimilars, despite small differences, were expected to be as safe and effective as the reference medicine [25]. This publication preceded previous documentation issued by the EC in 2014 explaining the concept of biosimilars to HCPs and the pharmaceutical industry [26]. Therefore, based on all the continually emerging evidence in favour of switching, the chief pharmacist and consultant gastroenterologist of the large acute Irish teaching hospital decided to switch all its patients from originator brand infliximab to biosimilar infliximab CT-P13 commencing in September 2016. This decision was relayed to all prescribing physicians during an internal staff meeting where the chief pharmacist and consultant gastroenterologist explained the science behind their evidence-based decision. All physicians accepted this and agreed to switch patients given the vast amount of evidence presented. Physicians agreed to report any ADRs to the HPRA and to EMA. Hospital budget coordinators were once again pleased. Although physicians found it more challenging to reassure patients of the switch at first, they reported that after informing and addressing all patient concerns at the point of prescribing, no opposition to switching arose.

In October 2016, explorative subgroup analyses of patients with CD and UC in the NOR-SWITCH study showed similarity between patients treated with originator infliximab and biosimilar infliximab CT-P13 with regard to efficacy, safety and immunogenicity [27]. Although this was one of the more large-

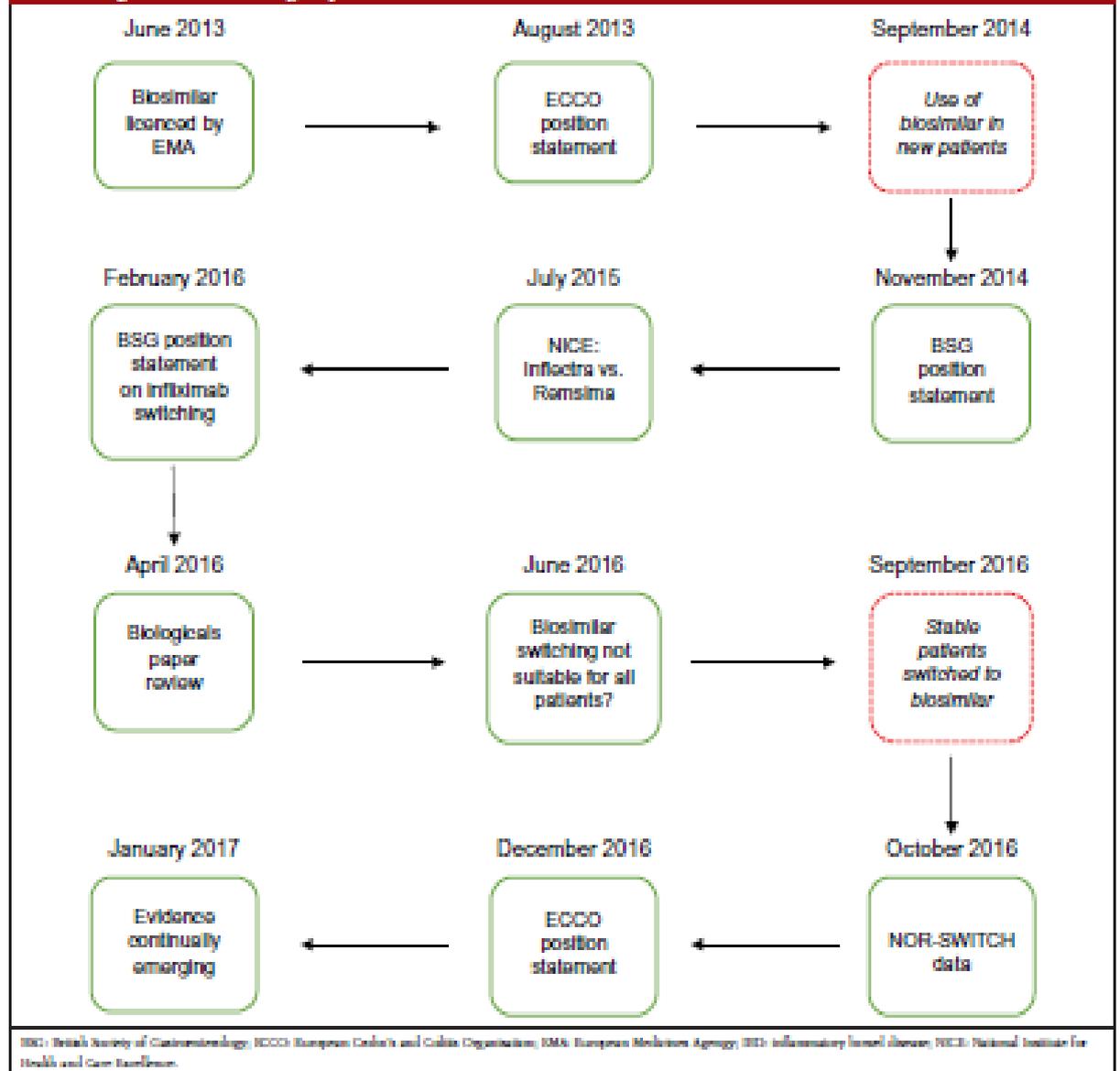
scale controlled studies where biosimilar infliximab CT-P13 was tested in IBD patients, the small sample size of the IBD subgroup was too small to demonstrate any difference in ADR identification or minor differences in effect [27]. However, it was still an advancement on previous evidence for switching which was more so justified on the concept of extrapolation. ECCO released an updated statement in December 2016 that revised its previous guidelines. One of the prominent recommendations was that switching IBD patients from the originator brand to a biosimilar product was now deemed acceptable. It also stated that studies of switching can provide valuable evidence for safety and efficacy and that scientific and clinical evidence is lacking regarding reverse switching, multiple switching, and cross-switching among biosimilars in IBD patients [28]. In this rapidly moving field, the evidence is continuing to grow supporting the case that biosimilar infliximab CT-P13 is just as safe and effective as the originator biological. Figure 1 illustrates in diagrammatic form, the systematic trail of evidence behind the decision-making process to introduce and switch patients to biosimilar infliximab CT-P13 in this large acute Irish teaching hospital.

Results and discussion

The decision to treat new and switch existing patients to biosimilar infliximab CT-P13 in this large acute Irish teaching hospital was a multifactorial one underpinned by a robust and extensive evidence-based trail that ultimately convinced prescribing physicians. From September 2014, all new patients requiring infliximab therapy for the treatment of IBD were prescribed biosimilar infliximab CT-P13. In September 2016, all IBD patients receiving Remicade® were switched to biosimilar infliximab CT-P13. Switching from originator infliximab to biosimilar infliximab CT-P13 in IBD patients occurred in this hospital before any other Irish hospital and before the release of the NOR-SWITCH study data. Biosimilar infliximab CT-P13 was first licensed in June 2013 [15] but it was not until approximately three years later that prescribers in this large acute Irish teaching hospital decided to switch patients. It is evident that there was a significant time lag between regulatory approval and clinical acceptance. In fact, Ireland has the second lowest record of biosimilar use due to Irish HCPs being slow to accept biosimilars [29, 30]. This is possibly owing to a lack of confidence, unwillingness or knowledge to prescribe biosimilars which is also seen in other European countries [31]. Work which aims to enhance the understanding of biosimilar medicines amongst stakeholders and to encourage best practice of biosimilar use is currently being conducted by a collaborative organization of various interested parties [32, 33]. However, it could be argued that Ireland has exceptionally low biosimilar uptake because biosimilar prescribing is not mandated unlike in other countries [34]. In addition, the Irish biosimilar market does not appear very appealing to pharmaceutical companies. Despite the potentially huge cost savings to be made from switching, only 54 packets of the biosimilar product Bene-pa® were sold since its introduction to Ireland in August 2016 compared to almost 46,856 of the established originator brand Entreb® (as of May 2017) [35]. Furthermore, various funding systems of different countries can too have an impact where, for example in the U.K, a major motivation for switching was reinvestment of some of the cost savings in improvements to patients' care [20].

REVIEW ARTICLE

Figure 1: Independent systematic evidence base behind the decision-making process to implement biosimilar infliximab CT-P13 in a large acute Irish teaching hospital for the treatment of IBD



The decision by this Irish teaching hospital to switch patients to biosimilar infliximab could have been regarded as over cautious, delayed and conservative given that EMA had already licensed the biosimilar medicine three years earlier [15] and thus, one wonders why prescribers had not switched patients sooner. With regard to the current biosimilar medicine landscape, it is possible that prescribers may feel more comfortable issuing biosimilars if national authorities would actively enforce and implement individual EMA biosimilar-related decisions as they are published. EMA has the best knowledge of biosimilars amongst regulators but cannot influence interchangeability that is within the mandate of individual national regulatory agencies [16].

These authorities have different capacities to produce information on biosimilars and as a result, this situation contributes to the differential rate of acceptance of biosimilars within EU Member States. With continually emerging positive evidence, it is clear that a three-year time lag for the next biosimilar medicine, from market authorization to the patient switching process, should not occur. *Aixabri[®]*, biosimilar infliximab SR2 [36], received market authorization approximately three years after biosimilar infliximab CT-P13 [37]. Given its late entry to the market relative to biosimilar infliximab CT-P13, it has been unsuccessful in penetrating the Irish market so far. The chief pharmacist and consultant gastroenterologist of this teaching

hospital note that they would not be comfortable in switching patients from biosimilar infliximab CT-P13 to biosimilar infliximab SB2 without conducting a comprehensive review of the available evidence, (especially evidence from a switching study), even if the national regulator did declare all licensed biosimilars completely interchangeable [11]. Interestingly however, this large acute Irish teaching hospital was content to switch patients to Tovagrastim®, a biosimilar of filgrastim [36], from the originator brand without performing such a robust evidence review. With regard to the difference between these medicines and their respective disease states, the onset of response on neutrophil count from filgrastim therapy occurs very quickly after administration and thus is routinely measured to ascertain treatment effectiveness. In contrast, there is no such clear-cut marker for assessing the onset of response from infliximab therapy at these very early stages so this is why an extensive evidence review was conducted prior to switching patients. The comparison between the implementation of these two biosimilars demonstrates that each biosimilar medicine requires a distinct and individualized approach when considering its introduction into the clinical setting; one approach does not suit all.

In the field of gastroenterology, biosimilar adalimumab, which is licensed to treat IBD, was recently granted market authorization [39]. In the Irish context to date, there have been no major efforts to introduce or switch patients to this biosimilar. However, adalimumab is predominantly dispensed by pharmacists in the primary care setting. This is in contrast to infliximab, which is commonly dispensed in the secondary care environment. This difference is quite interesting as it raises the issue that perhaps primary care pharmacists should be targeted by regulatory agencies to encourage patients to switch to biosimilar adalimumab in an effort to increase biosimilar medicine market penetration. However, as previously noted, this switch would have to be initiated by the prescribing physician [9] and be based upon appropriate evidence. Indeed, there are already many interesting and established approaches to biosimilar medicine implementation which demonstrate that just because a biosimilar medicine is licensed, does not mean that its use will be accepted by prescribers nor that all patients receiving the originator brand should be automatically switched. One such

approach is whereby the American National Kidney Foundation sponsored a symposium entitled 'Introduction of Biosimilar Therapeutics into Nephrology Practice in the United States' [40]. With anticipated increase in biosimilar products in the field of nephrology, mutually accepted lack of knowledge regarding the biosimilar approval process and development, and lack of trust with respect to biosimilar medicines' safety and efficacy, this community of experts decided to meet at a nationwide level to discuss the introduction of biosimilars into their area of medicine. The colloquium highlighted several controversies but also made recommendations related to public policy, professional and patient education, and research needs [40]. With the introduction of new biosimilars set to increase on the market in coming years [41], this example of individual fields of medicine taking responsibility for biosimilar usage pertaining to their area may be a safe, feasible and effective approach to introduce biosimilars into the clinical setting. This strategy might be particularly suitable for fields like oncology and other inflammatory diseases where biosimilar usage is set to increase substantially [42, 43]. Another possible approach is that original biological and biosimilar medicines can be prescribed on the proviso that patients will be entered into disease-specific registries. These registries may be used as surveillance systems for monitoring ADRs, as well as to quantify and evaluate the risk-benefit ratio throughout a medicinal product's life. Registries may be particularly effective for the evaluation of rare ADRs occurring in the real-world population of treated patients, as opposed to the highly selected populations in registration studies [44].

Following on from information released by the medicine management programme (MMP) on biosimilars in the Irish healthcare setting in 2016 [45], and guidance issued by the national cancer control programme (NCCP) on the use of biosimilar medicines in oncology in August 2017 [46], the Department of Health (DoH) disseminated a consultation paper in mid-August 2017 [29]. This paper indicates that the DoH is developing a national biosimilar medicines policy which aims to increase biosimilar use in Ireland by creating a robust framework where biologicals and biosimilars can be safely, cost-effectively and confidently used in the health service [13]. Table 1 reveals which topics of interest are being scrutinised. It is hoped this policy will address the inter-hospital

variation to biosimilar medicine implementation in Ireland and shorten the acceptance process of using biosimilars in the clinical setting. An interesting issue raised by the consultation paper is that of inappropriate business practices [13]. Although this was not of concern for this large acute Irish teaching hospital, impact of the source of information and collaboration of prescribers with the pharmaceutical industry can in principle, have an influence on originator product and biosimilar product prescribing

Table 1: Areas under investigation in the Irish biosimilar consultation paper

Prescribing and Interchangeability	By focusing on the remit of biological medicine prescribing, it is hoped that the low uptake of biosimilars in Ireland can be increased
International Biosimilar Medicines Policies	International policies are being examined to decide which policy, if any, could be implemented in the Irish context
Education and Supports	Educational programmes and supports are being researched from the perspectives of the patient, healthcare professionals and pharmaceutical suppliers
Incentives and Disincentives	Incentives such as gain-sharing agreements and disincentives like patient co-payment systems are being analysed
Tendering and Pricing Policies	Internal and/or external referencing pricing arrangements as well as the various types of tendering processes used in different countries are being probed for their suitability in the Irish setting
Prevention of Inappropriate Business Practices	In addition to inappropriate business practices previously highlighted, exploration of such professional misconduct is being carried out

REVIEW ARTICLE

patterns. The consultation paper highlights that France and Germany have laws banning physicians from receiving gifts from pharmaceutical companies. For biosimilar medicine uptake to increase and be maintained, the information and evidence used by prescribers must not be tainted with commercial interests.

One of the consultation paper's recurring themes is that there is too much money being spent on originator biologicals when there are cheaper, equally effective alternatives available. It highlights that only 11 biosimilars are currently reimbursable by the Irish healthcare system, while over Euros 200 million is spent each year on biological drugs that already have approved biosimilars or that will have available biosimilars throughout 2016 (13). It is clear that the potential cost savings to be accrued from switching to biosimilars can increase patient access to other new medicinal products. The Irish Pharmaceutical Healthcare Association (IPHA) framework agreement plans to save money on biological medicines (36, 47) where most of these medicines are reimbursed on Ireland's high-tech medicine scheme. This scheme has seen an increase in expenditure from Euros 177.49 million in 2005 to Euros 562.29 million in 2015 (48, 49). This prodigious level of pharmaceutical expenditure cannot be maintained. Research from the Irish National Centre for Pharmacoeconomics (NICE) has shown that when pharmaceutical companies submit budget impact analyses (BIAs) for new high-cost medicines such as biologicals, the majority of these high-cost medicines have a greater cost burden on the budget than what is forecasted in their BIAs (50, 51). This results in taxpayers spending more than anticipated. Thus, an increase in the uptake of biosimilar medicines would be a more sustainable approach to lower the Irish drug bill. One approach the DoH could take would be to establish gainsharing agreements at hospital level. Hospitals could be financially awarded for using biosimilars (26) or fiscally penalized for lack of utilization. Gainsharing agreements have already proven to be a powerful incentive in increasing biosimilar use at EU level (52). With respect to the Danish biosimilar landscape, their initial passive approach to switching actually led to an administrative order (34). Thus, another approach the DoH could adopt would be to introduce reference pricing of biological products which would accelerate the path to increased biosimilar usage (13). Reference pricing of SMCE medicines has already resulted in savings of millions of euro in the Irish primary care setting (30). Success of the use of biosimilar infliximab CT-P13 at University Hospital Southampton (53, 54) and in Norway and Denmark was observed, where biosimilar infliximab reached market penetration levels in excess of 90% (as of April 2016) (55). Such uptake resulted in substantial drug acquisition cost savings and subsequently increased patient access to the biosimilar medicine (22, 53). A recent report by QuintilesIMS™ has shown that the entrance of biosimilars into the market increases price competition while also generating price reductions for both biosimilar and reference products (56). However, this report stresses that if the problem of low biosimilar uptake is not appropriately managed in the long term, this could lead to fewer new biosimilars being developed, reducing overall competitive pressure.

Conclusion

This review examines the evidence used by a large acute Irish teaching hospital to safely and effectively introduce biosimilar infliximab CT-P13 into the gastroenterology care pathway.

There was a significant time lag between regulatory approval and clinical acceptance notwithstanding that EMA had granted market authorization for biosimilar infliximab CT-P13 three years prior to the initiation of this hospital's switching process. However, the conservative approach to biosimilar infliximab implementation discussed in the review is justified given the conflicting and changing evidence disseminated from various sources over this three-year period. Alternative approaches that could be used to increase biosimilar medicine adoption into healthcare environments have been suggested. Undisputedly, this review demonstrates that increased biosimilar medicine usage is of benefit to all stakeholders: increased access for patients, more treatment options for prescribers, sustainable healthcare budgets for payers and more business opportunities for manufacturers.

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8.8 Appendix VIII - Chapter 4 Publication



Cost-Effectiveness Analysis of a Physician-Implemented Medication Screening Tool in Older Hospitalised Patients in Ireland

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Abstract

Background A recent randomised controlled trial conducted in an Irish University teaching hospital that evaluated a physician-implemented medication screening tool, demonstrated positive outcomes in terms of a reduction in incident adverse drug reactions.

Objective The present study objective was to evaluate the cost effectiveness of physicians applying this screening tool to older hospitalised patients compared with usual hospital care in the context of the earlier randomised controlled trial.

Method We used a cost-effectiveness analysis alongside a conventional outcome analysis in a cluster randomised controlled trial. Patients in the intervention arm ($n = 360$) received a multifactorial intervention consisting of medicines reconciliation, communication with patients' senior medical team, and generation of a pharmaceutical care plan in addition to usual medical and pharmaceutical care. Control arm patients ($n = 372$) received usual medical and pharmaceutical care only. Incremental cost effectiveness was examined in terms of costs to the healthcare system and an outcome measure of adverse drug reactions during inpatient hospital stay. Uncertainty in the analysis was explored using a cost-effectiveness acceptability curve. **Results** On average, the intervention arm was more costly but was also more effective. Compared with usual care (control), the intervention was associated with a non-statistically significant increase of €877 (95% confidence interval – €1807, €3561) in the mean healthcare cost, and a statistically significant decrease of – 0.164 (95% confidence interval – 0.257, – 0.070) in the mean number of adverse drug reaction events per patient. The associated incremental cost-effectiveness ratio per adverse drug reaction averted was €5358. The probability of the intervention being cost effective at threshold values of €0, €5000 and €10,000 was 0.236, 0.455 and 0.680, respectively.

Conclusion Based on the evidence presented, this physician-led intervention is not likely to be cost effective compared with usual hospital care. To inform future healthcare policy decisions in this field, more economic analyses of structured medication reviews by other healthcare professionals and by computerised clinical decision support software need to be conducted.

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Key Points

A physician-implemented medication screening intervention based on the STOPP/START criteria demonstrated positive outcomes in terms of a reduction in adverse drug reactions in older hospitalised patients.

The physician-implemented intervention is not likely to be cost effective compared with usual care, unless the healthcare provider is willing to pay a large amount of money to prevent an adverse drug reaction.

Pharmacist and/or computerised clinical decision support systems employed to carry out such medication reviews may be a more cost-effective approach than acquiring a physician.

1 Introduction

Within the 35 member countries of the Organisation for Economic Co-operation and Development, people born today have an average life expectancy of 80.6 years [1]. Given this 10-year increase in life expectancy from just 45 years ago, the greatly expanded older person population is one of the most resource-consuming patient groups interfacing with healthcare systems in all Organisation for Economic Co-operation and Development countries [2]. This cohort is often exposed to inappropriate prescribing and polypharmacy [3, 4], which can frequently lead to adverse drug reactions (ADRs) [5, 6]. The increasing incidence of ADRs within the older population is a growing health problem [7]. It is estimated that approximately 2000 bed days are the result of an ADR at any one time and the total costs are likely to exceed £171 million annually for ADRs occurring during admission in the UK [8]. This cost rises to approximately £1 billion when all ADRs are taken into account [9]. Initiatives that enhance medication management in older people can ameliorate patient outcomes and attenuate unnecessary expenditure [10, 11]. Given that an estimated 57% of all ADRs are considered avoidable, it makes sense to invest in interventions to prevent ADRs, particularly in older people who are at the highest risk [12].

Structured and unstructured medication reviews in the hospital environment can be an effective means to optimise pharmacotherapy. However, there can be variability in the manner in which these reviews are implemented [13]. They are generally carried out on an ad-hoc basis and can differ depending on which healthcare professional performs the review [14]. The published literature has numerous examples of randomised controlled trials (RCTs) testing different interventions that have the common overarching

aim of improving prescribing in the older adult [15–17]. One trial in particular demonstrated a statistically significant reduction in serious ADRs [18]. However, there are only two published clinical trials that have used potentially inappropriate medication (PIM) or potential prescribing omission (PPO) criteria as a structured medication review intervention for the purpose of ADR prevention in high-risk hospitalised older adults [19, 20].

Both of these RCTs have employed the widely used STOPP/START (Screening Tool of Older Persons' Prescriptions/Screening Tool to Alert doctors to Right Treatment) criteria (Version 1) [21]. The fundamental aim of the STOPP criteria is to minimise medication-related adversity by highlighting and avoiding PIMs. The complementary aim of the START criteria is to minimise preventable therapeutic failures by highlighting PPOs and encouraging appropriate prescriptions if they are absent for no justified clinical reason [22]. One of these cluster RCTs applied a structured pharmacist review of medication, which was supported by a computerised clinical decision support system (CDSS). It resulted in significant reductions in ADRs [20] and proved cost effective [23].

The other cluster RCT involved a single time-point intervention in which patients had their medications screened according to the STOPP/START criteria by a physician. Instances in which STOPP and START "rules" had been contravened were highlighted to the attending medical team with advice to adjust the patients' prescriptions accordingly. This once-off application of STOPP/START criteria alongside usual pharmaceutical care resulted in a significant reduction in incident ADRs compared with similar older patients receiving usual pharmaceutical care only [19]. However, before adopting any medication optimisation technology, appraisal of its economic and budgetary impact is important. Notwithstanding the significant ADR attenuation that arose from the application of the STOPP/START criteria, [19] an economic evaluation of this intervention has not yet been undertaken. The aim of this study was to conduct a cost-effectiveness analysis of the physician-implemented structured medication review based on its application in a RCT in an older population that aimed to reduce incident hospital-acquired ADRs. This is the first economic evaluation of a physician-led intervention that is based on the application of the STOPP/START criteria.

2 Methods

2.1 Prevention of Adverse Drug Reactions in Older Hospitalised Patients Randomised Controlled Trial

Full details of the particular RCT methods are published elsewhere [19, 24]. In brief, the single-blinded RCT was conducted in an 810-bed university teaching hospital in the south of Ireland over a 13-month period between May 2011 and May 2012. This trial was cluster randomised with consultants from each speciality represented in each trial arm. Patients were randomised into either intervention or control groups based on the consultant with primary responsibility for their care during their hospital stay. The intervention arm consisted of 360 patients. The control arm included 372 patients. All patients in this study received the usual medical and pharmacist inpatient care, which consisted of full medication reconciliation and surveillance of prescription order sheets (independent of medical prescribers) with specific written advice attached to the prescription order sheets. The baseline characteristics and trial-related outcomes of the study population are presented (see Table 1). No significant differences existed between the groups in terms of age, functional status, cognitive function or number of medications at entry to the study [19]. Although there was a statistically significant sex imbalance between the groups, it is unlikely that this had a significant influence on the primary outcome results [19, 25].

A research physician applied the STOPP/START intervention to patients' medication lists within 48 h of admission. The intervention consisted of three elements. The first of these involved the research physician applying the STOPP/START criteria once only in each intervention group participant on the basis of the diagnoses documented in their case records and the list of prescribed drugs and doses at the time of study enrolment. The

second element involved the research physician discussing the presence of any STOPP/START-defined PIMs and/or PPOs with a senior member of the patient's attending team (i.e. senior residents or in most cases, consultants). Third, within 24 h of applying STOPP/START criteria, the research physician placed a printed report in the participant's case record, reinforcing the oral recommendations based on the specific criteria that applied in each case. The final decision regarding acceptance or rejection of STOPP and START criteria recommendations lay with the participant's attending senior medical staff. All patients aged ≥ 65 years admitted under the care of the medical or surgical services through the emergency department were considered eligible for inclusion. However, exclusion criteria were: (1) aged < 65 years, (2) admission directly to psychiatric services, intensive care unit, palliative care unit, specialist geriatric or clinical pharmacology services, (3) anticipated length of stay (LOS) < 48 h, (4) elective admission, (5) terminal illness and (6) refusal to participate.

2.2 Economic Evaluation

The economic evaluation consisted of a trial-based analysis conducted alongside the cluster RCT. The perspective of the Irish public healthcare provider, the Health Service Executive, was adopted with respect to trial-related costs and outcomes. Evidence on resource use and patient health outcomes was collected by the research physician during the course of the trial and a retrospective review of patient medical records was carried out. The time horizon for ADR evaluation was confined to patient discharge or 10-day follow-up, whichever was sooner; this was informed by average LOS for an elderly patient in the Irish hospital system at the time [26]. The average LOS for patients aged 65–74 years is 7.9 days and is 10.4 days for patients aged 75–84 years. The study was not designed to measure the medium/long-term impact of this intervention and discounting of costs or outcomes was not required owing to the limited follow-up

Table 1 Baseline characteristics and trial-related outcomes of the study population in the randomised controlled trial

Variable	Measure	Intervention (n=360)	Control (n=372)	P value
Age, years	Median (IQR)	80 (73–85)	78 (72–84)	0.100
Male	n (%)	130 (36.1)	187 (50.3)	0.001
Female	n (%)	230 (63.9)	185 (49.7)	0.001
Nursing home residents	n (%)	51 (14.1)	36 (9.6)	0.080
Total number of daily drugs	n	3147	3212	0.520
Distribution of drugs	Median (IQR)	9 (6–11)	8 (6–11)	0.710
Length of hospital stay	Median (IQR)	8 (4–14)	8 (4–14)	0.961
Hospital mortality rate	n (%)	11 (3.1)	9 (2.4)	0.535

IQR interquartile range

period. Moreover, missing/censored data were not an issue in this evaluation, as the follow-up was facilitated by a unique hospital number identifier and confined to a single centre over a short time period. Statistical analysis was conducted on an intention-to-treat basis, and in accordance with guidelines for conducting economic evaluations alongside cluster RCTs, [27], which require that both the correlation and clustering of the cost and effect data be explicitly considered.

2.3 Cost Analysis

Multiple cost components were included in the analysis and are described in Table 2. Costs are expressed in Euros (€) using 2012 prices (unless otherwise stated). The primary component was the cost of employing the research physician, who then held the post of specialist registrar (i.e. senior resident) physician in geriatric medicine, to implement the required intervention steps. The mid-point of the Health Service Executive specialist registrar physician pay scale was used and adjusted according to guidelines for conducting economic evaluation in Ireland [28, 29]. Salary was adjusted for employers' insurance cost, pension payments and general overheads. Based on experience-based opinion from the primary research team and estimates from the literature [30], it was assumed for the analysis that 40 min was an appropriate duration to assign for the trained research physician to apply the intervention.

The second component consisted of the associated follow-up time for senior members of patients' attending teams to discuss and decide upon the suggested STOPPWSTART recommendations. Based on experience-based opinion from the primary research team, it was assumed for the analysis that this took 7 min. The mid-point on the Health Service Executive consultant physician pay scale was used in the cost analysis. The third major component was the cost of

hospital inpatient stay; this cost was obtained from aggregated national data [31]. In general, micro-costing estimates for patients are preferable. However, in the context of this piece of research, the 24-h, national Irish hospital stay, average cost per patient was more pragmatic to use despite patients being admitted with a diverse range of primary indications. The fourth component consisted of the specialist registrar's training in the use of STOPPWSTART criteria. Interactive training courses given by the creators of the STOPPWSTART criteria generally last for approximately 4 h and were costed accordingly.

All resource use was valued using a vector of unit cost data presented in 2012 Euro (€) prices and summed to calculate a total cost variable for the statistical analysis given that the trial was completed in 2012. However, at the time of manuscript preparation (December 2017), the contemporaneously available healthcare costs (CAHC) in the Irish context were re-applied to the intervention steps. These costs are expressed in 2015 Euros (€) prices (unless otherwise stated) [see Table S1 of the Electronic Supplementary Material (ESM)]. Statistical analysis was re-run with the CAHC and original trial effectiveness data (see ESM2). This supplementary analysis was undertaken as a point of interest to examine the stability of medical inflation in Ireland during the post-financial crisis period.

2.4 Effectiveness Analysis

The primary outcome measure of this cluster RCT was the difference in the proportion of participants in the two arms experiencing one or more ADRs during index hospitalisation. Adverse drug reactions were identified by the research physician and a blinded second researcher. A comprehensive description of ADR identification and outcomes is provided elsewhere [19].

Table 2 Costs associated with the care of patients in the intervention arm in 2012

Cost component	Unit cost (€)	Description	References
Training of research physician in intervention criteria (once off)	0.56	Circa 240 min of training required costing approximately €200.00	Experience-based opinion from a primary research team
Research physician applying the intervention	2.50	Median time of 3 min to apply intervention [30]	HSE salary scales [29]
Research physician informing specialist consultant of intervention findings and answering related questions	5.83	Approximated time of 7 min (experience-based opinion from original research team)	HSE salary scales [29]
Specialist consultant being made aware and possibly implementing intervention findings	16.33	Approximated time of 7 min (experience-based opinion from original research team)	HSE salary scales [29]
Research physician compiling printed report of intervention findings	25.00	Approximated time of 30 min (experience-based opinion from original research team)	HSE salary scales [29]
Hospitalisation costs	820.00	24-h, national Irish hospital stay, average cost per patient	Healthcare Pricing Office [31]

HSE Health Service Executive

2.5 Cost-Effectiveness Analysis

In an economic evaluation, one health technology (treatment/intervention) is considered more cost effective than its comparator if it meets one of the following criteria [32]:

1. Less costly and more effective;
2. More costly but more effective, with an incremental cost-effectiveness ratio (ICER) that is considered acceptable by decision makers;
3. Less costly and less effective, but the additional cost per unit of effect of its comparator is not considered worth paying by decision makers.

In the context of the current study, we conduct a cost-effectiveness analysis to identify which of the three conditions applies here. Notably, the ICER represents the additional cost per unit effect, which in this case, is the additional cost of preventing an additional non-trivial ADR in secondary care. This raises the concern of what healthcare policy makers and decision makers in Ireland would be willing to pay to prevent an ADR. While threshold values exist for some generic measures such as quality-adjusted life-years, no such value per ADR prevented currently exists. In this analysis, we present our results in the context of a number of hypothetical thresholds, as previously proposed in the literature [23]. Recent work that compares methods for estimating direct costs of ADRs may inform a threshold value for ADR prevention in the future [33].

Statistical techniques were adopted to account for the effect of both clustering and correlation of cost and effect data collected alongside cluster RCTs [34]. The incremental analysis was undertaken using multi-level regression models for both the cost and effect data. Both models were estimated to control for treatment arm, age, sex, number of medications at admission and consultant (cluster group). The regression for the total cost variable was estimated using a multi-level, mixed-effects linear regression model and the regression for the ADR event variable was estimated using a mixed-effects logistic regression model. The estimated treatment arm effects represent the incremental costs and incremental effects for the intervention relative to the control. The 95% confidence intervals report the statistical significance of these coefficients based on standard errors estimated using the 'mixed' command in STATA[®] Version 13 (IBM SPSS Statistics 22; IBM Corporation, Armonk, NY, USA).

Uncertainty in the analysis was addressed by estimating confidence intervals and a cost-effectiveness acceptability curve (CEAC), which links the probability of a treatment being cost effective to a range of potential threshold values (λ) that the healthcare system may be willing to pay for an additional unit of effect [35]. Commonly, non-parametric bootstrapping can be conducted on the difference in mean

costs and mean ADRs to generate ICER replicates with which to construct a CEAC [36]. However, the CEAC in this analysis was estimated parametrically using the net benefit regression framework following the method proposed by Hoch et al. [37]. The CEAC explicitly presents the uncertainty relating to the threshold value coupled with the statistical variability inherent in trial data.

Finally, a series of scenario analyses was performed that varied the time required by all healthcare professionals to complete the intervention by $\pm 50\%$. The incremental cost-effectiveness analysis was re-run using CAHC and the original trial effectiveness data (see Table S2 of the ESM). The aim was to assess the cost effectiveness of this intervention if it was to be implemented in usual clinical care by hospitals today. Analysis was performed using STATA[®] Version 13 and Microsoft Excel[®] 2010 (Microsoft Corporation, Redmond, WA, USA).

2.6 Guidelines and Ethical Considerations

This article followed the Consolidated Health Economic Evaluation Reporting Standards guidelines for reporting health economic evaluations [38] (see Table S3 of the ESM) with joint reference to the published good research practices for cost-effectiveness analysis alongside clinical trials, i.e. the International Society for Pharmacoeconomics and Outcomes Research Task Force on Good Research Practices: Randomized Clinical Trials-Cost-Effectiveness Analysis report [39]. The original clinical cluster randomised trial conformed to Consolidated Standards of Reporting Trials guidelines [40]. The research ethics committee (institutional review board) of the local teaching hospitals network approved the trial protocol and the trial was registered with the US National Institutes of Health (NCT01467050). Written consent was sought and obtained from all participating patients, prior to enrolment in the original cluster RCT.

3 Results

The physician-led STOPP/START intervention resulted in a marked absolute risk and relative risk reduction for incident ADRs, i.e. 11.4 and 47.7%, respectively [19]. However, this was accompanied by an increased cost relative to usual medical and pharmaceutical care (see Table 3). The mean (standard deviation) cost of caring for an intervention patient during a single admission was €12,102 (€13,490). In the control group, the mean (standard deviation) cost of care was €11,160 (€12,506). Median costs were higher for the intervention group (€7430) compared with the control group (€7380). Following application of a multi-level mixed-effects model in STATA[®] Version 13 and accounting for baseline differences across both arms, the adjusted

Table 3 Incremental cost-effectiveness analysis using 2012 data

	Intervention group (n = 360)	Control group (n = 372)
Cost analysis		
Total healthcare cost (£)		
Mean (SD)	12,102 (13,490)	11,160 (12,306)
Effectiveness analysis		
Participants experiencing ≥ 1 ADRs [n (%)]		
	42 (11.67)	78 (20.97)
ADRs experienced per patient [n (%)]		
0	318 (88.33)	294 (79.03)
1	39 (10.83)	67 (18.01)
2	3 (0.83)	11 (2.96)
ADRs per patient [mean (SD)]	0.125 (0.356)	0.239 (0.492)
Incremental cost-effectiveness analysis		
Incremental cost		
Difference in mean healthcare cost (£) ^{a,b}	877 (95% CI – 1807, 3561)	
Incremental effect		
Difference in odds ratio for ADR events ^{a,c}	0.391 (95% CI 0.233, 0.657)	
Difference in mean ADR events ^{a,c}	– 0.164 (95% CI – 0.257, – 0.070)	
ICER per ADR averted (£)	5358	
Threshold value (£) per ADR averted (£)	Probability that intervention is cost effective ^d	
0	0.236	
500	0.255	
1000	0.275	
5000	0.455	
10,000	0.680	
20,000	0.926	

ADR adverse drug reaction, CI confidence interval, ICER incremental cost-effectiveness ratio, SD standard deviation

^aReported estimates for incremental differences in costs and effects adjusted to account for baseline differences between arms

^bRegression for total costs estimated using multi-level, mixed-effects linear regression models and controlling for treatment arm, age, sex, number of medications at admission and clustering

^cRegression for ADR event estimated using mixed-effect logistic regression models and controlling for treatment arm, age, sex, number of medications at admission and clustering

^dProbabilities for cost effectiveness estimated parametrically using net benefit regression models for analysis at each threshold value

incremental difference in cost of £877 was statistically non-significant.

In contrast, the effectiveness measures favoured the intervention strategy and were statistically significant. The odds ratio for a patient experiencing an ADR was 0.391 when comparing the intervention (STOPP/START) group to the control (usual hospital care) group. This related to an adjusted difference in the mean number of ADRs of – 0.164. Although the physician-implemented STOPP/START intervention was more costly, it too was more effective than usual clinical care. The calculated ICER was £5358 for the prevention of an ADR. However, as with all attempts to calculate the cost effectiveness of an intervention, there is a degree of uncertainty surrounding the ICER. Even if the healthcare payer was willing to pay the £5358 for the prevention of an ADR, the probability of the intervention being cost effective was 50%. There was a 92.6% probability that the

intervention would be cost effective if the healthcare payer was willing to pay £20,000 for the prevention of an ADR (see Table 3). When the cost-effectiveness analysis was rerun using CAHC and the original trial effectiveness data, the ICER underwent a slight increase to £5469 (see Table S2 of the ESM). Scenario analyses demonstrated that if healthcare professional times associated with the intervention were altered by $\pm 50\%$, this had a minimal effect on the original ICER estimate (see Table S4 of the ESM). This was also true of the scenario analyses that used CAHC and original trial effectiveness data (see Table S5 of the ESM).

The overall cost of applying the STOPP/START intervention to a group of 360 patients was estimated to be approximately €18,000 or €50 per patient. The majority of the intervention costs were associated with the expense of the research physician's time conducting the intervention (~ €33 per patient). Length of hospital stay was responsible

for the majority of the cost associated with management in both arms of the cluster RCT.

4 Discussion

It is unlikely that the physician-led STOPP/START intervention is cost effective. For instance, at a willingness-to-pay threshold of €10,000 per ADR averted, the probability of the intervention being cost effective is only 68%. If a significantly higher threshold of €20,000 is applied, the probability of the intervention being cost effective increases to 92.6%. The willingness-to-pay thresholds used in this analysis were arbitrary but when one considers that the mean cost associated with a single ADR event in secondary care has been estimated at €2250, [41], the threshold values presented in Table 3 are a reasonable measure of what could be considered value for money. This cited mean cost of a single ADR also suggests that it is unlikely decision makers would be willing to pay the quoted threshold values because a high probability of cost effectiveness is only reached at high threshold values. Similar increases in the cost of care could be imputed from this study, as patients who experienced an ADR had their median LOS increased by 3 days [19].

The principal barrier to the application of this intervention by a trained physician at a wider level is physician working hours' capacity. The senior resident research physician screened no more than four new patients each day for trial enrolment during the cluster RCT. It should be noted that the research physician was not employed on a full-time basis to apply the intervention to patients. If all older hospitalised patients were to receive this level of pharmaceutical care, increased staff numbers would likely be required. However, given the results from the analysis, it could be argued that the role of the specialist physician is to conduct all relevant medical duties in the secondary care environment. Although there are some published data in the primary care setting literature [42], we could find no reputable references dealing with economic analyses of physician-led medication-related interventions in the secondary care setting literature. Thus, it is difficult to align the results of this analysis with similar studies. One similar trial involving a research pharmacist conducting a similar medication review-based intervention supported by a computerised CDSS proved to be cost effective relative to routine hospital care [23].

A recent systematic review investigating the effectiveness and cost effectiveness of interventions aimed at preventing medication error (medicines reconciliation) at hospital admission demonstrated that the majority of these interventions are pharmacist led, not physician led [43] and that the pharmacist-led interventions are generally considered more cost effective than the respective study comparator [44]. In addition, two ongoing European multi-centre randomised

clinical trials, i.e. SENATOR and OPERAM [45, 46], implement the STOPP/START criteria using a computerised CDSS. A recent systematic review concluded that computerised interventions are associated with a significant reduction in potentially inappropriate prescribing in older hospitalised patients [47]. Computerised interventions in this field appear to reduce cost [48] and be cost effective [49]. It is also envisaged that the application of STOPP/START criteria in the SENATOR and OPERAM trials may prove less labour intensive and more cost effective than its application in the trial analysed in this study. Given all of this evidence, it is likely that the more clinically effective and cost-effective medication screening interventions in older hospitalised patients in the future will comprise pharmacist-led and/or computerised CDSS interventions.

A study conducted in Canada assessed the cost effectiveness of self- vs. physician-managed oral anticoagulant therapy over a 5-year period using a Bayesian Markov model [50]. Self-management resulted in fewer adverse drug events than physician management with the average discounted incremental cost of self-management relative to physician management calculated to be Can\$989 per patient with incremental quality-adjusted life-years of 0.07 gained [50]. Although this study did not assess medication screening in the elderly *per se*, it is yet another example of where a physician-implemented medication intervention was not found to be cost effective. Conversely, the literature once again appears to favour medication screening programmes involving or implemented by pharmacists. This point is supported by two recently published studies demonstrating the cost effectiveness of pharmacist-driven medication reviews towards optimisation in older patients [15, 51].

Notwithstanding the research physician's absence during medical rounds, the 83.4% acceptance rate of STOPP/START recommendations by attending doctors is noteworthy [19]. However, in a very similar analysis where the research pharmacist was absent during medical rounds, a lower acceptance rate of 38.5% by attending doctors was notable [52]. As the present analysis argues that pharmacist-led medication screening interventions are an effective and a cost-effective solution, the low rate of acceptance of pharmacist prescribing recommendations by attending physicians needs to be further investigated. In relation to pharmacist medication reviews, a robust method for economic evaluation of such medication assessments has been elucidated [53]. Ideally, the evaluation should be conducted with a 1-year follow-up period from a healthcare service provider viewpoint. Health-related quality of life is contended as the preferred effectiveness measure utilised, allowing correlation with confirmed societal values. The ultimate and most comprehensive appraisal would be a cost-benefit evaluation over a 5-year period from a societal perspective. Thus, if the standard practice model of medication reviews is to

be pharmacist led, the economic evaluation aspect of such reviews should be conducted using the proposed methods.

The cluster randomisation of the RCT that this evaluation is based upon resulted in a statistically significant sex imbalance between the control and intervention groups [significantly fewer women in the control group (49.7%) than in the intervention group (63.9%)]. Although sex imbalance in any RCT is not desirable, there is no evidence to indicate that sex had a significant influence on the prevalence rates of PIMs, PPOs or incident ADRs in the trial. The literature has shown that female individuals experience higher rates of PIMs and ADRs relative to male individuals [54–56]. Given the higher proportion of women in the intervention group, one would have expected higher rates of ADRs in this arm yet the results demonstrated the contrary. Therefore, it is unlikely that the sex imbalance between groups had a significant influence on primary outcome results. There were no other significant demographic differences between the two treatment arms. As stated, demographic analysis is presented in the original RCT paper [19].

It has been established that conducting economic evaluations based on data from RCTs is a suitable methodology [57]. This approach has two main advantages, i.e. (1) internal validity is maintained owing to the comprehensive nature of data collection during the trial and (2) there is a modest marginal cost associated with collecting required data from a trial that is predominantly clinically orientated [57]. While a cost-utility analysis with a health-related outcome measure is recommended as the reference case in the Republic of Ireland [28], it was not a realistic outcome measure for this analysis. The population under consideration had multiple co-morbidities and often an initially poor health status [19]. Therefore, health-related quality of life was not appropriate in this case [58]. Appropriate methods were used to investigate the cost-effectiveness analysis of the trial data. Multi-level mixed-effect models were chosen as they are an acceptable means for estimating the incremental net benefits for a clinical trial of this nature. Clustered data can potentially lead to biased results [59]. Normal statistical analyses are generally inappropriate; however, the methods employed for our analysis surmounted this issue [34]. These techniques account for both the clustering and correlation of cost and effect data.

4.1 Limitations

There are several limitations to this economic evaluation, principally pertaining to extrapolation of the findings to routine clinical practice. Training costs and time estimates were not recorded at the time of the event and were retrospectively informed by the primary research team. It is likely that some costs associated with this intervention may have been overestimated or underestimated. For example, the 7-min

time period allocated for discussion of STOPP/START recommendations could vary considerably depending on the number of recommendations generated and the subjective prescribing assessment thought processes of the attending consultant. In addition, the 30-min time period allocated to compiling the research physician's printed report could be replaced by a 5-min handwritten summary of recommendations into patients' medical records. However, the scenario analysis demonstrated that if healthcare professional time associated with intervention implementation was altered by 50% in both directions, this had a minimal effect on the original ICER estimate (see Table S4 of the ESM). Furthermore, a time-and-motion study, which gathers data on healthcare professional time required to complete the intervention, would have reduced uncertainty surrounding this input. As healthcare professionals become more familiar with the application of the STOPP/START criteria, they will be able to apply them more effectively and arrive at decisions at a faster rate.

Adverse drug reactions are often compared to icebergs [60]; those that are visible and identified, and those that are below the water's surface where neither patient nor intervening clinician recognise that they are drug effects, and thus unquantifiable. Therefore, it is possible that the amount of ADRs identified in both arms of the trial is not the true value. Depending on the type and severity of the ADR, the cost, patient LOS and overall impact on healthcare utilisation can vary dramatically [41, 61]. This level of detail was not reflected in our evaluation. Therefore, it is potentially dangerous to dismiss the intervention as not being cost-effective because the outcome at the time was not measurable or identifiable. There are also those that may be causing no symptoms or signs at the time but represent a real risk in the future. Ideally, a longer duration of follow-up for ADR evaluation would have been more preferable as it possibly could have allowed for further identification of ADRs.

Moreover, this evaluation is based on the work of one research physician in a single centre. Aspects of the intervention that would be variable between sites include the clinical experience of the research physician involved and the extent of the uptake of STOPP/START criteria recommendations by the receiving medical team. The attending physician is solely responsible for deciding whether the application of the STOPP/START criteria is clinically important or not. This is a subjective choice, irrespective of formal training. There are other examples of medication optimisation as a result of the application of the STOPP/START screening tool [22]. This single study site increased the possibility of crossover learning between healthcare colleagues within the secondary care environment. However, if healthcare decision makers are insistent about supporting and promoting physician-led medication screening interventions, this evaluation should be performed on a larger scale

involving multiple hospital sites as in the SENATOR and OPERAM trials [45, 46].

As stated, the trial was conducted in 2011/2012 and cost effectiveness was calculated using 2012 healthcare costs. When the analysis was re-run using CAHC and original trial effectiveness data, the cost of the intervention was marginally lower (see Table S1 of the ESM); however, there was a slight ICER increase that is attributed to the increased 24-h, national Irish hospital stay, average cost per patient (see Table S2 of the ESM). It is unlikely that healthcare policy decision makers would execute the rollout of this intervention today as it has become less cost effective recently. However, a budget impact analysis would have to be completed alongside the cost-effectiveness analysis to assess if policymakers were serious about its adoption [63]. In addition, the results of economic analyses based on RCTs must be interpreted with caution especially if there are limitations or flaws inherent in the trial design. However, the RCT that formed the basis of the present cost-effectiveness analysis achieved 80% power to detect a statistically significant difference in ADR incidence between the groups at the 95% confidence level [19]. It would have been interesting to calculate the incremental net benefit statistic to derive the same conclusion on cost effectiveness as that of the ICER. This was not possible because a willingness-to-pay threshold for ADRs has not yet been elucidated.

This is the first study to evaluate the economic impact of a physician-led medication review intervention based upon the STOPP/START criteria. Since their development in 2008 [21], STOPP/START criteria have become an extensively used method of identifying and improving instances of potentially inappropriate prescribing [52, 63]. This analysis provides further information about the adoption of STOPP/START guidelines as a fundamental part of any healthcare review conducted by a healthcare professional in an older population. The present analysis has implemented recommendations from the Consolidated Health Economic Evaluation Reporting Standards statement to ensure that this article presents a transparent high-quality evaluation.

5 Conclusion

Based on the information extracted from the cluster RCT, the physician-implemented medication screening tool based on the STOPP/START criteria is unlikely to be considered cost effective. The healthcare payer would have to pay €20,000 to attain a 92.6% probability that this intervention, which prevents ADRs, is cost effective. However, as the authors are unaware of decisions previously made based on the cost per ADR prevented, there is uncertainty regarding the cost-effectiveness status of the intervention from a policy perspective. Moreover, while the difference

in incremental effects on an individual basis did demonstrate statistical significance, the difference in overall incremental costs did not. To date, the literature appears to be sparse with regard to physician-implemented medication review interventions in secondary care in contrast with the multiplicity of studies describing pharmacist-led programmes, which appear to be clinically effective and budget positive [44]. At a minimum, this evaluation further adds to the growing body of evidence that a structured form of medication review and reconciliation incorporating STOPP/START criteria is superior to usual clinical practice. The present data suggest that a pharmacist with/without a CDSS designed for STOPP/START criteria employed to carry out such medication reviews may be a more cost-effective approach than a medication review by a specialist physician.

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Compliance with Ethical Standards

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Conflict of Interest: Stephen Byrne and Denis O'Mahony have part ownership in a patent "A Prescription Decision Support System" (based on STOPP/START prescribing rules); the patent was registered with the European Patent Office (Munich); Patent no. 11751930.8-1952. Stephen Byrne and Denis O'Mahony are also involved with two European Commission-funded grants that involve clinical trials in which there is computerised deployment of the STOPP/START criteria as part of an intervention designed to optimise pharmacotherapy in older adults. The first European Commission grant is called "Development and clinical trials of a new Software Engine for the Assessment and Optimisation of drug and non-drug Therapy in Older persons [SENATOR]", grant agreement 303930, awarded under the Seventh Framework Programme (FP7). The trial is registered with the US National Institutes of Health (NCT02097654). Denis O'Mahony is coordinator of the SENATOR project. The second European Commission-funded project is called "OPERAM: Optimising therapy to prevent Avoidable hospital admissions in the Multimorbid elderly". OPERAM is funded under the Horizon 2020 programme (HIC 17-2014). The OPERAM trial is based on another software intervention called "Screening Tool to Reduce Inappropriate Prescribing", which uses STOPP/START rules to assess the pharmacotherapy of older people. The trial is registered with the US National Institutes of Health (NCT02986425). Gary L. O'Brien, Paddy Gilheenan, Mark Mulcahy, Valerie Walsh, Marie N. O'Connor, David O'Sullivan and James Gallagher have no conflicts of interest that are directly relevant to the content of this article.

Ethics Approval The research ethics committee (institutional review board) of the local teaching hospitals network approved the trial protocol and the trial was registered with the US National Institutes of Health (NCT01467030).

Informed Consent Written consent was sought and obtained from all participating patients prior to enrolment in the study.

Journal of Economic Literature (JEL) Classification This article is classified as I19 according to the JEL system.

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8.9 Appendix IX - Chapter 4 Supplementary cost description

Costs associated with care of patients in intervention arm in 2015 (CAHC)

Cost Component	Unit Cost (€)	Description	Reference
Training of research physician in intervention criteria (once off)	0.56	circa 240 minutes of training required costing approximately €200.00	Experience-based opinion from primary research team
Research physician applying the intervention	2.50	Median time of three minutes to apply intervention (252)	HSE salary scales (403)
Research physician informing specialist consultant of intervention findings and answering related questions	5.83	Approximated time of seven minutes (Experience-based opinion from original research team)	HSE salary scales (403)
Specialist consultant being made aware and possibly implementing intervention findings	15.17	Approximated time of seven minutes (Experience-based opinion from original research team)	HSE salary scales (403)
Research physician compiling printed report of intervention findings	25.00	Approximated time of 30 minutes (Experience-based opinion from original research team)	HSE salary scales (403)
Hospitalisation Costs	839.00	24-hour national Irish hospital stay average cost per patient	Healthcare Pricing Office (404)
Key: HSE: Health Service Executive			

8.10 Appendix X - Chapter 4 Supplementary incremental cost-effectiveness analysis

Incremental cost-effectiveness analysis using CAHC and original trial effectiveness data

	Intervention group (n = 360)	Control group (n = 372)
Cost analysis		
Total cost (€)		
Mean (SD)	12,380 (13,802)	11,419 (12,795)
Effectiveness analysis		
Participants experiencing ≥ 1 ADRs [n (%)]	42 (11.67)	78 (20.97)
ADRs experienced per patient [n (%)]		
0	318 (88.33)	294 (79.03)
1	39 (10.83)	67 (18.01)
2	3 (0.83)	11 (2.96)
ADRs per patient [mean (SD)]	0.125 (0.356)	0.239 (0.492)
Incremental cost-effectiveness analysis	Intervention vs Control	
Incremental cost		
Difference in mean healthcare cost (€) ^(a,b)	895 (95% CI -1851, 3642)	
Incremental effect		
Difference in odds ratio for ADR events ^(a,c)	0.391 (95% CI 0.233, 0.657)	
Difference in mean ADR events ^(a,c)	-0.164 (95% CI -0.257, -0.070)	
ICER per ADR averted (€)	5,469	
Threshold value (λ) per ADR averted (€)	Probability that intervention is cost-effective ^(d)	
0	0.236	
500	0.255	
1,000	0.274	

Threshold value (λ) per ADR averted (€)	Probability that intervention is cost-effective ^(d)
5,000	0.450
10,000	0.672
20,000	0.921

Key: SD: standard deviation; ADR: adverse drug reaction; CI: confidence interval; ICER: incremental cost-effectiveness ratio

- (a) Reported estimates for incremental differences in costs and effects adjusted to account for baseline differences between arms
- (b) Regression for total costs estimated using multilevel mixed-effects linear regression models and controlling for treatment arm, age, sex, number of medications at admission and clustering
- (c) Regression for ADR event estimated using mixed effect logistic regression models and controlling for treatment arm, age, sex, number of medications at admission and clustering
- (d) Probabilities for cost-effectiveness estimated parametrically using net benefit regression models for analysis at each threshold value

8.11 Appendix XI - Chapter 4 Supplementary scenario analysis

Scenario analysis using CAHC and original trial effectiveness data

50% increase in healthcare professional time	Incremental Analysis - Intervention vs Control
Incremental Cost: Total Cost (€) <i>Difference in Mean</i>	918 (95% CI -1828, 3664)
Incremental Effect: No. of ADR Events (n) <i>Difference in Mean</i>	-0.164 (95% CI -0.257, -0.070)
Incremental cost-effectiveness ratio (€)	5,608
50% decrease in healthcare professional time	Incremental Analysis - Intervention vs Control
Incremental Cost: Total Cost (€) <i>Difference in Mean</i>	872 (95% CI -1875, 3620)
Incremental Effect: No. of ADR Events (n) <i>Difference in Mean</i>	-0.164 (95% CI -0.257, -0.070)
Incremental cost-effectiveness ratio (€)	5,330
Key: ADR: adverse drug reaction; CI: confidence interval	

8.12 Appendix XII - Chapter 4 Cheers checklist

Section/item	Item no	Recommendation	Reported on page no.
<i>Title and abstract</i>			
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	Pg 0
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Pg 1
<i>Introduction</i>			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Pg 2
<i>Methods</i>			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Pg 3
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Pg 2
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Pg 3
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Pg 2
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Pg 3
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Pg 4
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Pg 5
Measurement of effectiveness	11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Pg 5

Section/item	Item no	Recommendation	Reported on page no.
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A
Estimating costs and resources	13b	<i>Model-based economic evaluation:</i> Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Pg 4
Currency, price date and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Pg 5
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	N/A
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	N/A
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Pg 6
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	N/A
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Pg 8
Characterising uncertainty	20b	<i>Model-based economic evaluation:</i> Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Pg 7

Section/item	Item no	Recommendation	Reported on page no.
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A
<i>Discussion</i>			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Pg 10
<i>Other</i>			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Pg 12
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Pg 12

8.13 Appendix XIII - Chapter 5 Publication

Cost Minimization Analysis of Intravenous or Subcutaneous Trastuzumab Treatment in Patients With HER2-Positive Breast Cancer in Ireland

Gary L. O'Brien,¹ Cian O'Mahony,¹ Katie Cooke,² Ada Kinneally,³ Sarah-Jo Sinnott,⁴ Valerie Walshe,⁵ Mark Mulcahy,⁶ Stephen Byrne¹

Abstract

This study analyzed which route of trastuzumab administration, for the treatment of human epidermal growth factor receptor (HER)2-positive breast cancer, was more cost-effective and time-saving in relation to active health care professional time. In clinical practice, trastuzumab subcutaneous treatment resulted in greater cost and time savings compared with trastuzumab intravenous treatment. At present, trastuzumab subcutaneous treatment should be considered a clinically equivalent and more cost-effective option to trastuzumab intravenous treatment.

Background: Two large acute Irish University teaching hospitals changed the manner in which they treated human epidermal growth factor receptor (HER)2-positive breast cancer patients by implementing the administration of trastuzumab via the subcutaneous (SC) route into their clinical practice. The study objective is to compare the trastuzumab SC and trastuzumab intravenous (IV) treatment pathways in both hospitals and assess which route is more cost-effective and time saving in relation to active health care professional (HCP) time. **Materials and Methods:** A prospective observational study in the form of cost minimization analysis constituted the study design. Active HCP time for trastuzumab SC- and IV-related tasks were recorded. Staff costs were calculated using fully loaded salary costs. Loss of productivity costs for patients were calculated using the human capital method. **Results:** On average, the total HCP time saved per trastuzumab SC treatment cycle relative to trastuzumab IV treatment cycle was 59.21 minutes. Time savings in favor of trastuzumab SC resulted from quicker drug reconstitution, no IV catheter installation/removal, and less HCP monitoring. Over a full treatment course of 17 cycles, average HCP time saved accumulated to 16.78 hours, with an estimated direct cost saving of €1609.99. Loss of productivity for patients receiving trastuzumab IV (€15 days) was greater than that of trastuzumab SC (€60 days) for a full treatment course. **Conclusion:** Trastuzumab SC treatment has proven to be a more cost-effective option than trastuzumab IV treatment that generated greater HCP time savings in both study sites. Healthcare policymakers should consider replacing trastuzumab IV with trastuzumab SC treatment in all eligible patients.

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Keywords: Administration routes, Cost analysis, Micro-costing, Oncology, Outpatient care

Introduction

Breast cancer is the most common cancer in women.^{1,2} The humanized monoclonal antibody trastuzumab is indicated for the treatment of both early and metastatic human epidermal growth

factor receptor 2-positive (HER2⁺) breast cancer.³ In this group of patients, trastuzumab is administered every 3 weeks for 1 year (either 17 or 18 treatment cycles, depending on the decision of the attending physician) in early breast cancer or, in the case of

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metastatic breast cancer until disease progression, by intravenous (IV) infusion at a dose calculated according to the patient's weight.³ The duration of administration for trastuzumab IV in this condition is 90 minutes in the first administration (loading dose) and 30 minutes for consecutive treatment administrations (maintenance dose).³ In addition to the IV formulation, a subcutaneous (SC) formulation exists. It has an administration time of less than 5 minutes and is given by a single-use injection device (SID) or via handheld syringe (HHS). The dose is independent of the patient's weight. The SC formulation has demonstrated pharmacokinetics, efficacy, and a safety profile comparable to the IV formulation in patients with early HER2⁺ breast cancer in the coHAnced treatment with NeoAdjuvant Herceptin (HamaH) trial.⁴ Both the safety and tolerability of subcutaneous trastuzumab for the adjuvant treatment of Human epidermal growth factor receptor 2-positive early breast cancer (SubHer) trial and the Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PreHer) trial have also corroborated these findings.^{5,6}

There are 2 general approaches to costing health care: top-down and bottom-up. A top-down approach estimates the cost of an individual service on average, usually using routinely available data (eg, average per diem cost). Top-down costing studies tend to be relatively quick and straightforward to conduct; however, they are also less precise and cannot provide information on individual factors driving the costs.⁷ Disease-specific per diem costs (or daily cost) give the average daily cost for treatments in each disease category but may still be quite broad.⁷ Case-mix groups yield the cost for each category of "case" or hospital patient and take length of stay into account. While this approach to costing is more precise than the aforementioned approaches, a bottom-up approach (micro-costing) generates more precise estimates but is more onerous to perform. In micro-costing, all resources used are identified and then the unit cost of the resources are multiplied by the quantities used.⁷ Studies examining the differences between the cost estimates produced by both top-down and bottom-up approaches have concluded that bottom-up approaches are preferable for estimating cost components that have a large impact on total costs (eg, labor, expensive drugs), for services where there is wide variation in costs between patients, and for centers that are integrated within a larger hospital compared with independent centers.⁸⁻¹¹

Trastuzumab IV was first launched in Ireland in December 2000, whereas trastuzumab SC was launched in December 2013.¹² The release of trastuzumab SC came at an interesting time when Ireland began to restructure its health care funding system from one where hospitals are funded based on historical levels of funding adjusted for activity and patient mix to a prospective case-based payment system (Activity Based Funding).¹³ This change is currently being implemented for in-patient and day-case activity and will subsequently include outpatient services.¹³ Within the Activity Based Funding system, previously referred to as "Money Follows the Patient," prices will be set initially with reference to average prices, but with an overall aim to implementing best practice prices on an incremental basis.¹³ Therefore, with respect to the contemporaneous reform in the Irish health care sector, the aim of this study was to estimate the total cost of providing trastuzumab treatments in 2 large acute Irish University teaching hospitals within the south-

east coast hospital group in the year 2018. The perspective of the Irish health care service provider was adopted, using a micro-costing approach, and the unit of productivity was calculated from a societal perspective. In the Irish context, this is the first economic evaluation examining the impact of switching trastuzumab formulations.

Materials and Methods

Hospital 1 – Nurse-led Clinic

Hospital 1, a 431-inpatient and 85-day procedure bed teaching hospital, provides general medical, surgical, and emergency care to approximately 0.5 million patients of southeast Ireland. This hospital is the designated cancer center for southeast Ireland. In 2011, a group of patients in this hospital entered into the SubHer trial.³ In early 2014, this hospital began to switch patients from trastuzumab IV to trastuzumab SC and decided to introduce a dedicated trastuzumab SC clinic for patients with HER2⁺ breast cancer. The approach of moving this cohort of patients out of the day oncology ward attempted to improve the patient journey. This hospital took the decision to resource the trastuzumab SC clinic with a dedicated clinical nurse specialist (CNS), rather than share the resource with the oncology day ward. Clinic times ran from 09:30-16:00 where each patient receives an allocated 45-minute treatment slot with a 1:1 patient to nurse ratio.

Hospital 2 – Infusion Clinic

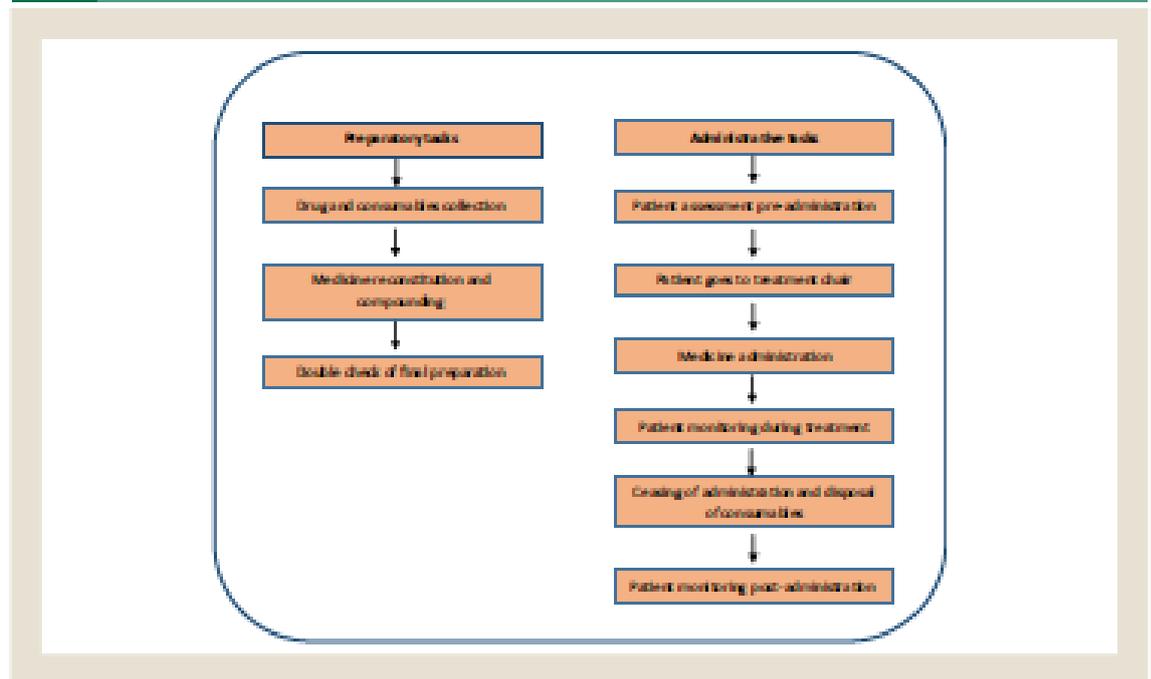
Hospital 2 is a teaching hospital in the south of Ireland that has a designated bed complement of 192 beds and cares for up to 38,400 admissions and 72,500 outpatient attendances each year. In late 2015, the pharmacy department in this hospital made the decision to switch patients from trastuzumab IV to trastuzumab SC. Patients are given either a morning or afternoon appointment in the infusion clinic at this hospital, where they are attended to on a first come, first served basis by a clinical nurse specialist upon entry into the patient log.

Cost Minimization Analysis

We conducted a prospective observational study in a subgroup of health care professionals (HCPs) and patients with HER2⁺ breast cancer that attended both University hospitals between May and June 2018. All data were collected by GOR, COB, AK, and KC. Both hospitals were each visited on 4 occasions between April and June 2018. Each observation consisted of measuring the time required to perform a specific task related to the preparation and administration of trastuzumab. To quantify active HCP time, the time actively involved in carrying out the tasks when differences between the routes of administration had been predicted, was observed. Figure 1 shows the tasks that both trastuzumab SC and IV treatment pathways have in common where time estimates were recorded. Patients receiving adjuvant trastuzumab treatment were included. All observations were made using a stopwatch. Patient treatment room times (time between entrance and exit from treatment room), were inferred from active HCP times. Although not enough sample time estimates were recorded for each task to run a time and motion study, the estimates gathered were verified by the HCPs involved in the study as being a true reflection of average time spent on tasks in routine clinical practice. An average time for each task was subsequently calculated and used in the cost analysis. This methodology has been previously seen in the

Cost Minimization Analysis of Trastuzumab Treatment Administration Routes

Figure 1 Common Tasks Conducted in the Preparation and Treatment of Trastuzumab SC and IV



Abbreviations: IV = intravenous; SC = subcutaneous.

instances.^{14,15} When a sufficient amount of time estimates were recorded for a particular HCP activity associated with trastuzumab preparation, compounding, and administration, a Student *t* test was performed for the 2 groups. In all these instances, results were statistically significant (*P* values < .05). Overall, a micro-costing approach was adopted.

Direct and indirect costs were calculated. Direct costs included HCP costs for the tasks observed (nurses, pharmacists, and pharmacy technicians), costs of consumables, and drug costs. Indirect costs included the cost of lost productivity. Although both hospitals had been using trastuzumab SC since 2015, intravenous only available health care costs, expressed in Euros (€) using 2018 prices (unless otherwise stated), were chosen. These updated costs provide a more accurate representation of current spending in the health care sector and are more useful in the preparation of a budget impact analysis, if required.¹⁶ The perspective of the Irish public health care provider, the Health Service Executive (HSE), and the societal perspective were adopted. Evidence on resource use and patient health outcomes were collected by the research team during the course of the study, and a retrospective review of patient medical records was conducted. However, this was of no major concern in this study given that both trastuzumab formulations are clinically equivalent.⁶ That inclusion for the study was less than 2 months, thus discounting was not required. Multiple cost components were included in the analysis and are described. The mid-points of the HSE health care professional pay scale was used and adjusted according to guidelines for conducting economic evaluation in Ireland.^{17,18} Salary was adjusted for employer's insurance costs, pension payments, and general overheads

(Table 1). Although the switching process in hospital 1 began in 2014 and in hospital 2 in 2015, the 2018 unit cost estimates were deemed appropriate for the analysis as medical inflation in Ireland was relatively stable during this period.

The costs of consumables were determined by reviewing invoices issued from the finance department from one of the large acute Irish University teaching hospitals in 2018 and calculating units cost¹⁹ (Table 2). Drug costs were calculated according to the 2017 reported ex-factory prices (exclusive of value added tax [VAT]) of trastuzumab IV 150 mg (€567.69) and trastuzumab SC 600 mg (€1645.24).²⁰ The medicinal brand of trastuzumab used in both hospitals was Herceptin, and patients were administered the trastuzumab SC formulation via a SID.⁹ All calculations were performed taking an average patient weight of 72.05 kg (average weight

Table 1 Costs of Health Care Workers

Job Description	Gross Annual Salary, € ^a	Total Costly, € ^b	Total Cost/min, €
Pharmacist	48,071	87,179	0.60
Pharmacy technician	38,447	53,730	0.48
Clinical nurse specialist	52,363	73,219	0.65
Staff nurse	37,508	52,417	0.47

^aApril 2018 Revised Health Service Executive Graded Pay scales.¹⁸

^bThe mid-point of the Health Service Executive pay scale was used and adjusted according to guidelines for conducting economic evaluation in Ireland.¹⁷

Table 2 Costs of Consumables in Patients Treated With Trastuzumab IV or Trastuzumab SC During a Treatment Cycle

Different Stages of a Complete Treatment Cycle	Cost of Preparing 441-mg Dose (3 × 150-mg Vials) of Trastuzumab IV, € (72.05 kg Patient ^{1.44})		Cost of Preparing a 600-mg Dose of Trastuzumab SC, ¹ €	
	Number of Items	Cost Ex-VAT	Number of Items	Cost Ex-VAT
Pre-cleaning of LAF				
70/30 IPA wipes	8	7.04	0	0
Preparation				
70% alcoholic wipes	20	1.40	14	0.98
70/30 IPA wipes	8	7.04	8	7.04
Shops bin	1	1.35	1	1.35
Sterile surface mats	2	2.80	2	2.80
Chemo protect gowns	1	4.67	1	4.67
Face masks	1	0.68	1	0.68
Hand gloves	0	0	2	0.04
Elbow length sterile gloves	1	2.10	0	0
Head cap	1	0.02	1	0.02
Mitt grip bags	1	0.08	1	0.08
Compounding				
Trastuzumab 150-mg vial ³	3	1669.01	0	0
Water for injection 10-ml cartridge	3	0.27	0	0
10-ml syringe	1	0.12	0	0
Pink needle	2	0.04	0	0
Seal for infusion bag	1	0.05	0	0
Sodium chloride 0.9% 250-ml bag	1	0.79	0	0
30-ml syringe	1	0.30	0	0
70/30 sterile wipes	4	0.28	1	0.07
Clickchemo labels	2	0.04	2	0.04
Flag label	0	0	1	0.04
Green poly bags	1	0.08	1	0.08
Trastuzumab 600-mg vial	0	0	1	1645.24
5-ml syringe compatible with the closed system device	0	0	1	1.24
Vertical vial access device/adapter 20-mm	0	0	1	1.74
Cost of running LAF ⁴	1	0.05	0	0
Administration				
Orange needle	0	0	1	0.02
Sodium chloride 10 ml	0	0	1	0.07
Sterile swabs	0	0	1	0.08
Hand gloves	2	0.04	2	0.04
Fabric plasters	1	0.03	1	0.03
Alcoholic 2% chlorhexidine wipes	1	0.02	0	0
Rubber arm band	1	0.45	0	0
Canula	1	0.70	0	0
Rubber bung for canula	1	0.84	0	0
Securing tape	1	0.23	0	0
Opaque infusion giving set	1	5.83	0	0
Sodium chloride 50 ml	2	1.30	0	0

Cost Minimization Analysis of Trastuzumab Treatment Administration Routes

Table 2 Continued

Different Stages of a Complete Treatment Cycle	Cost of Preparing 441-mg Dose (3 × 150-mg Vials) of Trastuzumab IV, € (72.05 kg Patient ^{23,24})		Cost of Preparing a 600-mg Dose of Trastuzumab SC, ^a €	
Equipment Needed	Number of Items	Cost Ex-VAT	Number of Items	Cost Ex-VAT
Post-cleaning of LAF				
70/30 IPA wipes	8	7.04	0	0
Total cost (including VAT)		1714.27		1666.31
VAT on injectables and all consumables 23% VAT rate ^{25,27}		304.40		383.25
Total cost (including VAT)		2108.17		2049.56

Abbreviations: IPA = isopropyl alcohol; IV = intravenous; LAF = laminar air flow unit; SC = subcutaneous; VAT = Value Added Tax.
^aThe National Adult Height Survey, which provides average weights, was used in the cost of preparing trastuzumab IV (females: age 25-50 years = 70.5 kg, age 51-64 years = 73.6 kg, that is mean weight for these prevalent age categories found with human epidermal growth factor receptor 2-positive breast cancer is 72.05 kg.²³
^bDrug banding information on trastuzumab IV provided by the National Cancer Control Programme for a 72.05-kg patient required 441-mg of drug (assume vial strength drug wastage) at a minimum a dose of 6 mg/kg²³ (initial loading dose was excluded). A 430-mg dose is prepared in clinical practice to obtain 441-mg of drug.
^cCost of consumables were retrieved from invoices provided by the finance and resource department of the hospital.²⁴
^dAverage cost of using a LAF to 600 seconds a per HCP (trastuzumab reimbursement time when a conversion rate of 1 United States Dollar equals 0.85 Euro as of June 2018 is applied).²⁸ Trastuzumab IV was compounded by aseptic technique in the LAF. Trastuzumab SC was reconstituted orally on the bench using the closed system for immediate administration.

in Irish women aged 36-64 years²⁷) treated with trastuzumab for 17 twice-weekly dosing cycles according to the data sheet guidelines, where 17 cycles is considered 1 year of treatment's full treatment cycle. Patient weights were retrieved from ClinixChem pharmacy management software. Patients' date of birth and gender were retrieved from LPM (i.Patient Manager). In line with the standard clinical practice, all vials were considered used (vial sharing) in patients treated with trastuzumab IV, resulting in no drug wastage. The effect of possible differences between reported and financed price was assessed in a sensitivity analysis where discounts of 15% in the ex-factory price of the vial of trastuzumab IV and between 15% and 20% in the ex-factory price of trastuzumab SC were applied. These rates are believed to mimic national current commercially sensitive transactions offered by pharmaceutical manufacturers on biological medicines to Irish hospitals and are corroborated by the literature.^{26,27} The effect of differences in the weight of patients was analyzed in another sensitivity analysis in which the cost of treatment in patients weighing between 65 and 75 kg were calculated. Vial sharing (no drug wastage) and dose banding tables from the National Cancer Control Programme (NCCP)²³ were used in association with the recommended twice-weekly maintenance dose of 6 mg/kg of body weight for trastuzumab IV.²³

Indirect costs were estimated using the human capital method²⁸ for inferred patient treatment room time. As applied in health care evaluation, the human capital approach has largely been used to value changes in the amount of time individuals are able to allocate to paid work as a result of illness or programs to alleviate ill health.²⁹ According to this approach, the gross wage becomes the unit of value for changes in paid working time resulting from health care programs.²⁹ In the context of this study, where the health care program, trastuzumab treatment, aims to reduce the patient's overall mortality risk, the change in productivity cost is represented by the present value of the stream of additional days in paid work over the duration of the patient's treatment cycle where each day is valued using the gross wage. The average income liable for social insurance in Irish women aged 15 to 84 according to the Irish Department of

Social Protection and Revenue Commissioners data, adjusted according to current (2018) consumer price index inflation, (€27206.40)^{30,31} was used in conjunction with the average recorded unemployment rate for Irish women aged 25 to 74 as of 2017 (5.4%),³² and the average hours worked by women per week in paid employment in 2016 (31.7 hours).³³

Guidelines and Ethical Considerations

This manuscript followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines for reporting health economic evaluation³⁴ (see Supplemental Table 1 in the online version). Ethical approval for this study was obtained from the clinical research ethics committee (institutional review board) of the local teaching hospital network.

Results

Direct Costs

Cost of Consumables. The cost of consumables per treatment cycle was €56.28 for trastuzumab IV and €25.91 for trastuzumab SC, a difference of €30.37 excluding the drug costs. For a complete 17-cycle treatment, the cost would be €956.76 for trastuzumab IV and €440.47 for trastuzumab SC, resulting in a saving of €516.29 per patient (Table 2).

HCP Cost. On average, the cost of HCP time invested in the preparation and administration of trastuzumab was €44.93 per cycle of trastuzumab IV and €9.83 per cycle of trastuzumab SC (Tables 3 and 4). For a complete 17-cycle treatment, this would result in a cost of €763.81 for trastuzumab IV and €167.11 for trastuzumab SC, with a cost differential of €596.70. Extrapolating these results to a hospital treating 25 patients per year with trastuzumab, as per hospital in this study, the total HCP cost would be €19,095.25 if all patients received trastuzumab IV and €4177.75 if all received trastuzumab SC, with an average saving of €14,917.50 (-78%) favorable to trastuzumab SC.

Table 3 Cost Description Associated With Trastuzumab Subcutaneous Preparation, Compounding, and Administration

HCP Activity	Recorded Time Estimate in Hospital 1, sec	Unit Cost, €	Recorded Time Estimate in Hospital 2, sec	Unit Cost, €
Pre-check of prescription by pharmacist	55	0.55	53	0.53
Medicine preparation by pharmacy technician			54	0.43
Pharmacist double check of medicine			10	0.10
ID, blood pressure, temperature, pulse, blood tests, weight, and ECG check by CNS	342	3.71	331	3.59
Staff nurse double check of medicine	55	0.43		
Tray preparation for drug administration by CNS	15	0.18	10	0.11
CNS preparation (gloves and gowning)	108	1.17	113	1.22
Patient preparation (caps swabbed with alcohol wipe) by CNS	15	0.18	12	0.13
Medicine preparation by CNS	45	0.49		
Injection administration time by CNS	310	3.38	280	3.03
Patient after care (wipe and plastic) by CNS	20	0.22	25	0.27
Total	965 (16.08 min)	10.25	888 (14.80 min)	9.41
Average HCP time of both hospitals	1544 min		Average HCP cost of both hospitals	9.83

Abbreviations: CNS = clinical nurse specialist; ECG = electrocardiogram; HCP = health care professional; ID = identifier.

Drug Costs. In the base case (reported ex-factory price inclusive of a VAT rate of 23%²⁰ and a national average patient weight of 72.05 kg²¹), the total cost of a 17-cycle treatment would be €34,893.97 for trastuzumab IV and €34,401.97 for trastuzumab SC, resulting in a difference of €497.00. In the first sensitivity analysis (discount of 15% for trastuzumab IV and a range of discounts from 15% to 20% for trastuzumab SC), the cost difference between treatments ranged from €1027.84 to €2747.98 in favor of trastuzumab SC. In the subsequent sensitivity analysis (considering patient weights between 65 and 75 kg and where handled down for trastuzumab IV, recommended by the NCCP, were applied²²), the cost difference

between treatments ranged from €–2826.71 to €497.00. More extreme weights (ie, patients ≥ 80 kg) could reach savings greater than €3820.71.

Indirect Costs

The average patient treatment room time in our study sites was 841 seconds for trastuzumab SC and 3052 seconds for trastuzumab IV (assuming no waiting times for patients). Estimated indirect costs according to bed productivity informed by patient treatment room time for a 17-cycle treatment per patient were €243.74 (bed of 2.15 working days) for trastuzumab IV and €67.15 (bed of 0.60 working days) for

Table 4 Cost Description Associated With Trastuzumab Intravenous Preparation, Compounding, and Administration

HCP Activity	Recorded Time Estimate in Hospital 1, sec	Unit Cost, €	Recorded Time Estimate in Hospital 2, sec	Unit Cost, €
Pre-check of prescription by pharmacist	119	1.19		
Pre-check of prescription and tray materials by pharmacist			307	3.07
Preparation of medicine tray and alcohol wipe down of items by pharmacy technician	243	1.94	122	0.98
Compounding of medicine by pharmacy technician in LAF	998	7.98	882	7.08
Pharmacist double check of medicine	150	1.50	33	0.33
ID, blood pressure, temperature, pulse, blood tests, weight, and ECG check by CNS	351	3.80	372	4.03
Staff nurse double check of medicine	54	0.42	49	0.38
Tray preparation for drug administration by CNS	182	1.97	200	2.17
CNS preparation (gloves and gowning)	102	1.11	99	1.07
Patient preparation (cannulation) by CNS	401	4.34	345	3.74
Injection administration by CNS	1800	19.50	1800	19.50
Patient after care (wipe and plastic) by CNS	182	1.97	167	1.81
Total	4592 (76.57 min)	45.72	4376 (72.93 min)	44.14
Average HCP time of both hospitals	7485 min		Average HCP cost of both hospitals	44.93

Abbreviations: CNS = clinical nurse specialist; ECG = electrocardiogram; HCP = health care professional; ID = identifier; LAF = laminar air flow unit.

Cost Minimization Analysis of Trastuzumab Treatment Administration Routes

Table 5 Total Costs in Patients Treated With Trastuzumab IV or Trastuzumab SC

Costs	IV, €	SC, €	Difference, €
Direct costs	36,619.54	35,009.55	1609.99
Healthcare professional costs	763.8	167.11	596.70
Consumable costs	958.28	440.47	517.80
Drug costs	34,898.97	34,401.97	497.00
Indirect costs	243.24	67.15	176.09
Total costs	38,683.28	35,076.70	1786.58

Abbreviations: IV = intravenous; SC = subcutaneous.

trastuzumab SC. Trastuzumab SC resulted in lower indirect cost per patient compared with trastuzumab IV.

Total Costs

Direct costs were €36,619.54 for trastuzumab IV and €35,009.55 for trastuzumab SC, a net difference of €1609.99 in favor of trastuzumab SC. When indirect costs were added, replacement of trastuzumab IV by trastuzumab SC for a full 17-cycle treatment would save €1786.58 (see Table 5).

Discussion

This study describes active HCP time invested in the preparation and administration of trastuzumab. A time saving of 79% is recorded by the replacement of trastuzumab IV with trastuzumab SC. In fact, the authors believe this is the highest recorded active HCP time saving, when other studies report time savings of 51% in Spain, 48% in Canada and Russia, 36% in France, 31% in Denmark, and 15% in Switzerland.¹⁹ Greater available HCP time could result in improvements in the quality of care, with more time free for monitoring, other relevant medical duties, or indeed providing patient information or comforting. In addition, by utilizing trastuzumab SC in the place of trastuzumab IV, a saving of €596.70 per patient in active HCP time for a full 17-cycle treatment is gained. This result is consistent with those of international studies.^{16,19}

The reduction in patient treatment room time resulted in a difference in indirect costs of €176.59 per 17-cycle treatment in favor of trastuzumab SC, a conservative estimate that only considered lost productivity between entering and leaving the patient treatment room. Moreover, this reduction in patient treatment room time could allow the treatment of the same number of patients with fewer resources or more patients with the same resources. As well as the economic implications, quality of life may improve with the time savings associated with trastuzumab SC. Indeed, a key finding of the ProHer study was that patients favored trastuzumab SC as it seemed to save more time used for them relative to trastuzumab IV treatment.⁶ Hence, more than just an estimate of cost from the social perspective, according to preferences enjoyed, we see that the patients can be the main beneficiary. Quality of life is especially important to those patients with metastatic breast cancer as theirs is a chronic illness and so minimizing the time spent in hospital is an important factor in survivorship.

Drug cost savings from switching to trastuzumab SC may be underestimated in this study. The National Adult Nutrition Survey was used in the cost of compounding trastuzumab IV (Women: age 36-50 years = 70.5 kg, age 51-64 years = 73.6 kg; thus, the mean weight for these prevalent age categories found with HER2⁺ breast cancer is 72.05 kg). This average weight is an underestimate of the true patient weight in Ireland (elderly a rising obesity problem).²⁰ The mean patient weight between both centers was 73.44 kg, with a range of 43.5 kg to 125 kg. Therefore, by using the average recommended weight of 72.05 kg, the trastuzumab IV formulation may appear less costly than it actually is in practice. As per sensitivity analysis, drug costs for trastuzumab IV are currently lower than drug costs for trastuzumab SC for patients only for patients weighing ≤ 69 kg. For patients weighing ≥ 70 kg, drug costs for trastuzumab IV begin to drastically increase relative to drug costs for trastuzumab SC.

In addition, for the recommended weight of 72.05 kg, a maintenance trastuzumab IV dose of 6 mg/kg² would require 432.3 mg of drug. This is rounded to 441 mg according to the national dose banding table²¹ provided by the NCCP. This results in 9 mg of drug remaining after each trastuzumab 150 mg vial reconstitution. Over 17 triweekly cycles, this equates to 153 mg of drug remaining. In this study, we assume vial sharing and no drug wastage. However, in clinical practice, it is unlikely this amount of drug would be utilized, as 9 mg of drug is a very small quantity to share at each treatment cycle juncture, and vial sharing opportunities do not always arise upon reconstitution. Therefore, it is possible that the cost of 17 triweekly cycles of the trastuzumab IV is appearing €712.22 cheaper per patient than it actually is. A loading dose of 8 mg/kg is required for patients when starting trastuzumab IV therapy or if patients miss their scheduled dose of trastuzumab IV by more than 1 week.² This presents an additional cost for trastuzumab IV that was omitted in this analysis. There is no initial loading dose for starting treatment or missed treatment with trastuzumab SC,²¹ resulting in this formulation being a more cost-effective option under these circumstances.

The main limitation of the study was that not enough time estimates were recorded to conduct a time and motion analysis. Although the estimates gathered were verified by the involved HCPs as being a true reflection of average times spent on tasks in routine clinical practice, a time and motion study, which gathers data on HCP time required to complete the observed tasks, would reduce uncertainty surrounding such inputs. As per other time and motion studies investigating this trastuzumab formulation switch, it would have been desirable to record hospital time (time between entry and exit from the hospital), and patient travel to the hospital, or the time lost by accompanying persons, by means of patient interview when calculating indirect costs.²⁶ These measurements would capture a broader societal perspective. Two recent time and motion studies have demonstrated that a transition to both trastuzumab and trastuzumab SC formulations from their respective IV formulations resulted in saved patient chair and active HCP time.^{25,27}

This study was carried out in only 2 centers where differences in clinical practice exist. As times, it was difficult to compare clinical practice procedures for the analysis. However, as this study was conducted in routine clinical practice settings yielding real world data, as opposed to a study within/alongside a randomized

controlled trial, the results are more generalizable. This study's design and setting may also explain why the active HCP time savings value of 79% is numerically higher than those corresponding values reported by time and motion studies conducted within open-label randomized crossover studies.³³ Nonetheless, as trastuzumab SC gains traction in the Irish health care setting, further research in more hospital sites should be conducted to corroborate these study findings.

At the time of data collection, one of the 46 patients receiving trastuzumab treatment was male. However, as the epidemiology of women with HER-2 breast cancer is much greater in women than men,³⁵ indirect costs and loss of productivity were calculated using statistics based on data gathered for Irish women. If this method was calculated for men, it is likely the indirect costs and loss of productivity would be greater based on data gathered for Irish men.³⁵

A potential limitation in this study is the issue of "dead time" (ie, the 5-minute time period required for trastuzumab IV to dissolve upon reconstitution⁵ and its 30 minute infusion time). Although it is potentially possible that the HCP could conduct other medical duties during this dead time, such tasks were impossible to cost. The issue of dead time and potential medical opportunity cost is a controversial one in the field of costing.⁴⁴ In addition, as best clinical practices are adopted in these 2 large Irish University teaching hospitals (eg, vial sharing), it was observed that the CNS upheld their duty of care by monitoring patients closely during the 30 minute trastuzumab IV infusion period for fear of adverse drug reactions, which limited their ability to perform other activities in parallel.

For trastuzumab IV, patients should be observed for at least 6 hours after the start of the first infusion and for 2 hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms.⁵ For trastuzumab SC, patients should be observed for 6 hours after the first injection and for 2 hours after subsequent injections for signs or symptoms of administration-related reactions.⁴⁵ Follow-up time was excluded from the cost minimization analysis, as no cost differential existed. In clinical practice, patients were strongly advised to remain in clinic for the recommended follow-up time, but this was seldom adhered to by patients. This variability in follow-up time from patients was not measured, which means the loss of productivity may be underestimated in this study. Parenteral treatment (by mouth or by IV infusion) was recommended for both trastuzumab IV and SC treatment cycles. Therefore, as no cost differential exists, it too was excluded from the cost analysis. As with follow-up time, there was unpredictability in this variable too, where some patients would take parenteral and some patients would refuse.

As present, it can be argued that this study is *only of interest* to hospital budget decision-makers within the acute/tertiary west hospital group in Ireland. This issue also arose in a similar study where the results of an economic evaluation of propofol/fentanyl compared with midazolam/fentanyl on recovery in the intensive care unit following cardiac surgery was *only of interest* to the local hospital.⁴⁶ However, more Irish hospitals are beginning to use trastuzumab SC, and following the successful implementation of trastuzumab SC in Europe, Oceania, and South America,^{26,44,47} it is envisaged this formulation will penetrate the North American oncology landscape next. Furthermore, in relation to the current oncology field,

biosimilar trastuzumab IV is now available.⁴⁸ It has been approved in Ireland since June 2018, where the biosimilar trastuzumab IV 150-mg vial Herzmira yields a drug cost of €4401.86 (exclusive of VAT).⁴⁹ This is in comparison to the Herceptin IV 150-mg vial, which yields a drug cost of €567.69 (exclusive of VAT).²³ The individual summary of product characteristics for both medical products appear almost identical^{48,49}; thus, it can be assumed that medicine reconstitution and administration tasks are equivalent, meaning the only major differential between the 2 products is the drug acquisition cost. It is also worth noting that local commercially sensitive price reductions are sometimes offered to payers who switch to biosimilar medicines.⁵⁰ It will be interesting to see what impact biosimilar trastuzumab will have on the Irish and international markets.

SC versions of different oncology therapies have been available for patients for a while now; however, it is only recently that patients-relevant and hospital benefits are being assessed.^{50,51} Although open to debate, the literature seems to be favoring SC oncology treatments over IV oncology treatments in terms of patient preference and time and cost savings.^{4,23,25,26,32,37} A recent International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Special Task Force report identified and defined a series of elements that warrant consideration in value assessments of medical technologies.⁵² In the report, Lakdawala et al discuss that some medical technologies offer advantages over existing alternatives such as simpler dosing schedules, alternate routes of administration, or combination treatments. To the extent that these improve patient adherence to treatments and health outcomes, they may impact the estimation of the value of the medical technology in the aggregate.⁵⁴ It is evident from this study that the trastuzumab SC formulation offers this advantage over the trastuzumab IV formulation. Trastuzumab SC also reduces the need for cannulation of patients whose veins are often compromised owing to previous therapies and toxic.

In this study, we attempt to capture the societal perspective by calculating the loss of productivity via the human capital method as well as presenting the more common health care payer perspective. Sanders et al recommended for the sake of consistency and comparability, analysts should report "reference cases" from 2 perspectives—the health care sector perspective and the societal perspective.⁵³ This was also corroborated by an ISPOR Special Task Force report.⁵⁶ In addition, Olsen and Richardson argue that the part of productivity effects may be included to the extent that it results in increased resources available for health care.⁵⁷ In fact, if the trastuzumab SC formulation was taken out of the secondary care setting and supplied to patients via their local pharmacy for self-injection at home, the loss of productivity would virtually be eliminated as patients could avoid going to hospital. In conjunction, this would alleviate some of the workload that the exhausted secondary care system already encounters. Ireland has devised a 10-year plan for health reform through political consensus called *Sláinte*, which is currently underway.⁵⁸ Its aim is to establish a universal, single-tier health service where patients are treated solely on the basis of health need but it also plans to re-orient the health system "towards integrated primary and community care that is consistent with the highest quality of patient safety in as short a time-frame as possible."⁵⁹ In line with the overarching aim of *Sláinte*, the

Cost Minimization Analysis of Trastuzumab Treatment Administration Routes

replacement of trastuzumab SC treatment to the primary care sector would also satisfy patient needs in terms of a preference for home- and community-based medical treatments.⁴⁰

Accurate cost data are essential for ensuring breast cancer services are effective, efficient, and equitable, and costing information should be used to guide policy, planning, and implementation in this field. This is particularly pertinent in the current situation in Ireland, as health care funding is undergoing restructuring.¹⁵ As demands on the service increase owing to greater numbers of patients⁴¹ and more complex cases, the cost data presented in this analysis will be available for cost-effectiveness evaluations of new drugs, technologies, and models of care. This is the first study to evaluate the economic, financial, and clinical impact of switching from trastuzumab IV to trastuzumab SC in Ireland. The present study has implemented recommendations from the CHEERS statement to ensure that this manuscript presents a transparent high-quality evaluation.

Conclusion

In conclusion, the replacement of trastuzumab IV by trastuzumab SC within 2 large acute Irish teaching hospitals has proven to be a more cost-effective approach reducing active HCP time and patient treatment room time, and therefore improving patients' quality of life. With respect to the Irish health care landscape, these reductions in time result in economic savings, more efficient resource use, and improved quality of care. Trastuzumab SC reduces the cost of consumables. Dependent on the patient's weight and the hospital's policy on vial sharing, trastuzumab SC did not always result in drug cost savings. A full treatment cycle of trastuzumab SC results in total estimated direct cost savings of €1609.99. Every year, between 400 and 500 new cases of HER2⁺ breast cancer present in Ireland,⁴¹ where such patients would be potentially eligible for treatment with trastuzumab. The widespread use of trastuzumab SC for these patients would not only result in direct cost savings but would also lead to a reduction in indirect costs owing to a decrease in the loss of productivity. These clinical and economic aspects demonstrate that trastuzumab SC results in benefits for patients, HCP, and indeed, wider society.

Clinical Practice Points

- In line with the current evidence, trastuzumab is the standard of care for HER2⁺ breast cancer.
- The trastuzumab SC formulation has demonstrated pharmacokinetics, efficacy, and a safety profile comparable to the IV formulation.
- There is an increasing body of literature that favors the use of trastuzumab SC over trastuzumab IV.
- In the Irish context, total HCP time saved per trastuzumab SC treatment cycle relative to trastuzumab IV treatment cycle was 59.21 minutes. Time savings in favor of trastuzumab SC resulted from quicker drug reconstitution, no IV catheter insertion and removal, and less HCP monitoring.
- The average HCP time saved summed to 16.78 hours, with a total estimated direct cost saving of €1609.99. Loss of productivity for patients receiving trastuzumab IV (2.15 days) was

greater than that of trastuzumab SC (0.60 days) for a full treatment course.

- Globally, active HCP time savings were similar to those reported in this study. Countries in Europe accumulated active HCP time savings as high as 51%, whereas Canada cumulated time savings of 36%.
- When available, SC administration of trastuzumab is preferable in terms of cost effectiveness, patient convenience, and satisfaction, and should be recommended over IV administration of trastuzumab when possible.

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Disclosure

The authors have no conflicts of interest to declare.

Supplemental Data

Supplemental table accompanying this article can be found in the online version at <http://dx.doi.org/10.1006/j.dcc.2019.01.011>.

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8.14 Appendix XIV - Chapter 5 Cheers checklist

Section/item	Item no	Recommendation	Reported (Yes/No)
<i>Title and abstract</i>			
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	Yes
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Yes
<i>Introduction</i>			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Yes
<i>Methods</i>			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Yes
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Yes
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Yes
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Yes
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Yes
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Yes
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	N/A
Measurement of effectiveness	11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	N/A
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A
Estimating costs and resources	13b	<i>Model-based economic evaluation:</i> Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Yes

Section/item	Item no	Recommendation	Reported (Yes/No)
Currency, price date and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Yes
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	N/A
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	N/A
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	N/A
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	N/A
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Yes
Characterising uncertainty	20b	<i>Model-based economic evaluation:</i> Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Yes
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Yes
Other			

Section/item	Item no	Recommendation	Reported (Yes/No)
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Yes
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Yes

8.15 Appendix XV - Chapter 5 Ethical approval



UCC

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Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee

Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

CREC Review Reference Number: ECM 4 (u) 05/06/18

Date: 16 May 2018

Professor Stephen Byrne
School of Pharmacy
Room 1.02
Cavanagh Pharmacy Building
University College Cork

Study Title: Quantitative analysis of respiratory sputum samples from patients admitted to Mercy University Hospital over a 16 month period, a trend analysis.

Approval is granted to carry out the above study at:

Mercy University Hospital.

The following documents have been approved:

Document	Approved	Version	Date
Cover Letter	Yes contains errors		20 April 2015? And also refers to an application dated November 2017
Application Form	Yes		16 April 2018
CV for Chief Investigator	No		
Evidence of Insurance	Yes		18 April 2018
Study Protocol	None		
Data Collection Sheet	None		
Participant Information Leaflet	Not applicable		
Consent Form	Not applicable		
Study Questionnaire/Survey	Not applicable		
Interview Guide	Not applicable		

We note that the co-investigator(s) involved in this project will be:

Name	Occupation
Frank O'Riordan	Antimicrobial Pharmacist
Aoife Fleming	Research Pharmacist
Jennifer Ake	Postgraduate Student.

The date of this letter is the date of authorization of the study.

Please keep a copy of this signed approval letter in your study master file for audit purposes.

You should note that ethical approval will lapse if you do not adhere to the following conditions:

1. Submission of an Annual Progress Report/Annual Renewal Survey (due annually from the date of this approval letter)
2. Report unexpected adverse events, serious adverse events or any event that may affect ethical acceptability of the study



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University College Cork, Ireland

3. Submit any change to study documentation (minor or major) to CREC for review and approval. Amendments must be submitted on an amendment application form and revised study documents must clearly highlight the changes and contain a new version number and date. Amendments cannot be implemented without written approval from CREC.
4. Notify CREC of discontinuation of the study
5. Submit an End of Trial Declaration Form and Final Study Report/Study Synopsis when the study has been completed.

Yours sincerely

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

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.



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CREC Review Reference Number: ECM 4 (t) 05/06/18

Date: 16 May 2018

Professor Stephen Byrne
School of Pharmacy
Room 1.02
Cavanagh Pharmacy Building
University College Cork

Study Title: Quantitative analysis of medical records from breast cancer patients admitted to Irish oncology units over a 30 month period, a trend analysis.

Approval is granted to carry out the above study at:

South Infirmary Victoria University Hospital
University Hospital Waterford.

The following documents have been approved:

Document	Approved	Version	Date
Cover Letter	Yes contains errors		20 April 2015? And also refers to an application dated November 2017
Application Form	Yes		20 April 2018
CV for Chief Investigator	No		
Evidence of Insurance	Yes		21 April 2018
Study Protocol	None		
Data Collection Sheet	None		
Participant Information Leaflet	Not applicable		
Consent Form	Not applicable		
Study Questionnaire/Survey	Not applicable		
Interview Guide	Not applicable		

We note that the co-investigator(s) involved in this project will be:

Name	Occupation
Gary O'Brien	Postgraduate Student
Cian O'Mahony	Postgraduate Student.

The date of this letter is the date of authorization of the study.

Please keep a copy of this signed approval letter in your study master file for audit purposes.

You should note that ethical approval will lapse if you do not adhere to the following conditions:

1. Submission of an Annual Progress Report/Annual Renewal Survey (due annually from the date of this approval letter)
2. Report unexpected adverse events, serious adverse events or any event that may affect ethical acceptability of the study



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Yours sincerely

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8.16 Appendix XVI - Chapter 6 Publication



Contents lists available at ScienceDirect

Health Policy

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Out of pocket or out of control: A qualitative analysis of healthcare professional stakeholder involvement in pharmaceutical policy change in Ireland



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ABSTRACT

Background: Mandatory co-payments attached to prescription medicines on the Irish public health insurance [General Medical Services (GMS)] scheme have undergone multiple iterations since their introduction in October 2010. To date, whilst patients' opinions on said co-payments have been evaluated, the perspectives of community pharmacists and general practitioners (GPs) have not.

Objective: To explore the involvement and perceptions of community pharmacists and GPs on this pharmaceutical policy change.

Methods: A qualitative study using purposive sampling alongside snowballing recruitment was used. Nineteen interviews were conducted in a Southern region of Ireland. Data were analysed using the Framework Approach.

Results: Three major themes emerged: 1) the withered tax-collecting pharmacist; 2) concerns and prescribing patterns of physicians; and 3) the co-payment system – impact and sustainability. Both community pharmacists and GPs accepted the theoretical concept of a co-payment on the GMS scheme as it prevents moral hazard. However, there were multiple references to the burden that the current method of co-payment collection places on community pharmacists in terms of direct financial loss and reductions in workplace productivity. GPs independently suggested that a co-payment system may inhibit moral hazard by GMS patients in the utilisation of GP services. It was unclear to participants what evidence is guiding the GMS co-payment fee changes.

Conclusion: Interviewees accepted the rationale for the co-payment system, but reform is warranted.

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Abbreviations: ACE, Angiotensin Converting Enzyme; COREQ, consolidated criteria for reporting qualitative research; DoH, Department of Health; FEMPS, Financial Emergency Measures in the Public Interest; GMS, General Medical Services; GP, General Practitioner/Physician; HCP, Healthcare Professional; HSE, Health Service Executive; IT, information technology; LT, long term illness; NHS, National Health Service; PCRS, Primary Care Reimbursement Services; PRN medicines, Pro re nata (as required) medicines; Sinn Féin, An Irish left-wing Irish republican political party; Taoiseach, Irish Prime Minister; UK, United Kingdom; WHO, World Health Organisation.

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1. Introduction

According to the World Health Organisation (WHO), a co-payment (user charge or user fee) is defined as "money people are required to pay at the point of using health services covered by a third party such as the Government, a health insurance fund or a private insurance company" [1]. These out-of-pocket fees are paid by the insured patient on many health services such as outpatient visits, dental care, and inpatient care and prescription medicines. There are many documented advantages in having a co-payment attached to prescription medicines: cost containment, moral hazard prevention and revenue generation [2]. Disadvantages include lower rates of drug treatment, worse adherence among existing users, more frequent discontinuation of therapy and increased

patient financial responsibility [3,4]. Co-payments are a common feature of Western health care systems [1].

The General Medical Services (GMS) scheme in Ireland is a tax funded, means tested, public health insurance scheme [5]. It provides many health benefits including inpatient and outpatient care, General Practitioner (GP) services and prescription medicines to those who meet the eligibility criteria [6], all free at the point of access. Currently, 33 % (1,565,048) of the Irish population receive healthcare on this scheme [7]. Patients who avail of health coverage on the GMS scheme are known as medical card holders. In October 2010, in an attempt to counteract rising Government expenditure amid a severe economic downturn post 2008, and to reduce medicine wastage, the Department of Health (DoH) introduced a €0.50 co-payment per prescription item, capped at €10 monthly, for the first time for publically insured (GMS) patients [8]. Since then, the GMS prescription medicine co-payment, also known as the GMS levy, has undergone numerous iterations in both monetary value per prescription medicine and in monthly cap fee (capped after the first 10 prescription medicines per month for each of the GMS co-payment iterations). Indeed, this levy is a form of taxation. Fig. 1 below reveals a timeline of all recent GMS co-payment changes where in March 2017: the introduction of different co-payments for separate age groups was first introduced on this scheme.

In the Irish context, patients were mostly accepting of the initial €0.50 co-payment with some reservations concerning an increased price and the way in which generated revenue would be used by Government [8]. This aligns with international patient perspective where most patients accept paying toward medication in principle [9–11]. Contemporary quantitative analysis on the GMS co-payment increases (Fig. 1) has demonstrated that the €0.50 co-payment was associated with reductions in adherence ranging from –2.1 % to –8.3 % for essential medicines and reductions in adherence of –2% to –9.5 % for less-essential medicines [12]. The €1.50 co-payment generally resulted in smaller reductions in adherence to essential medicines with anti-depressant medications being the exception with a decrease of –10.0 % after the co-payment increase [12]. For publicly insured families with children, a detrimental effect on health was not found from small co-payments (€0.50, €1.50 and €2.50) on prescription items [13].

The objective of the study was to retrieve insight into the engagement and opinions of experienced Healthcare Professionals (HCPs) on the GMS co-payment policy changes. Using the qualitative data collected from interviews, this manuscript aims to inform healthcare policymakers on this specific pharmaceutical policy as Ireland is currently in the process of attempting to deliver whole system reform and universal healthcare known as *SínteCare* for all its citizens [14]. This study adds to the literature by investigating the stakeholder involvement of HCPs in co-payments attached exclusively to prescription medicines, which to date, has not been researched.

2. Methods

2.1. Study design, setting and sampling

The sampling frame for this study was registered community pharmacists and GPs who had been consistently practising for at least six months prior to the first GMS co-payment introduction in October 2010 until data collection completion. Nineteen semi-structured interviews (thirteen community pharmacists, 6 GPs) were conducted between January 2018 and April 2019 where HCPs working in five different socioeconomic areas were interviewed in the province of Munster, Ireland (Table 1). Both community pharmacies and medical surgeries were classified into their respec-

Table 1
Distribution of practices by location and ownership status [15].

Practice Location	Independent	Franchise	Total
Affluent	2	1	3
Marginally above average	7	2	9
Marginally below average	2	0	2
Disadvantaged	2	2	4
Very Disadvantaged	1	0	1
Total	14	5	19

tive socioeconomic classes via the *Tritz Hasse Deprivation Index 2016* by electoral division [15]. HCPs from both independent and franchise pharmacies were included. Franchise pharmacies were defined those consist of several similar businesses which are corporately owned. All medical surgeries in this study were independently owned. Most interviews were conducted in an urban practice save for two marginally above average medical surgeries and one marginally above average community pharmacy which can be considered rural [16]. Varying socioeconomic and work place structures and locations were included to ensure that a broad range of thoughts and attitudes could be obtained from a range of social circumstances, age, gender, and work place practices. All interviewees declared they had no obvious bias to declare on this topic. This was asked to ensure that selection was not based on prior knowledge of interviewee involvement on this topic.

Interviewing was chosen as the preferred data collection method for many reasons. First, given that some of the interviewees owned their own pharmacy/medical surgery, the topic of work place practices, medicines, and money/financial loss can be considered a sensitive subject. Secondly, focus group dynamics can be unpredictable where more in depth coverage, with a lower risk of social desirability bias, is possible when interviewing an individual [17]. Consent form and participant information letters are made available (see online appendices 1, 2). Participants were sampled using purposive and snowball-sampling methods [17,18]. An initial 'core set' of potential participants were identified by the research team through personal contact. These participants were then asked to suggest other individuals they believed could assist with the study. Participants were free to decline the invitation to partake but did this not happen. Once HCPs agreed to be interviewed, the interviewer explained who they were, clarified the aims and objectives of the study and assured participants of anonymity and data confidentiality. Participants were asked for verbal and written consent. The researchers sought to address reflexivity during all aspects of the study.

2.2. Data collection

Two very similar topic guides were developed in order to achieve structured feedback from participants (see online appendix 3). One topic guide was targeted at the community pharmacists whilst the other was used when interviewing GPs. Given that both topic guides were designed to have a strong resemblance, data from both community pharmacists and GPs were analysed together as one combined HCP data pool. Both topic guides drew on existing related literature [8,12,19–24] and the professional experience of the research team. The topic guides were initially piloted with two pharmacists and one GP and were amended as the interviews progressed to obtain current and topical feedback from participants. The decision was made to exclude the pilot interviews from the analysis. The pharmacist topic guide underwent four iterations whereas the GP topic guide under two iterations. Many themes were discussed with both pharmacist and GP participants where some of these are highlighted in Table 2. All interviews consisted of one interviewer and one interviewee and were recorded and transcribed verbatim using two methods of audio recording: a Dic-

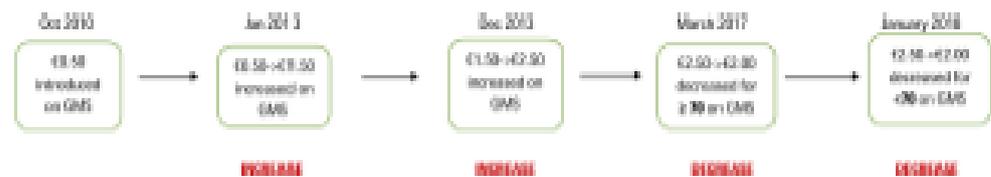


Fig. 1. Timeline review of recent GMS co-payment introductions and changes 2010–2018.

Table 2

Themes discussed in interviews.

Positive/negative aspects of co-payment?	What are your thoughts on the co-payment attached to prescription medication?
Influence of co-payments on your practice and procedures?	Has the co-payment influenced your practice or procedures in the work place?
Co-payment retrieval?	How easy or difficult is it to retrieve the co-payment?
Patients' perception of co-payment?	How do you think patients perceive paying the co-payment?
Financial loss?	Have you suffered financial loss from patients not paying?
Medicine utilisation?	Do you think the co-payment has influenced patients' utilisation of medication?
Impact of co-payments on GPs prescribing habits?	Has the co-payment changed the way you prescribe or influence the amount of prescriptions you issue?
Future status of co-payment/policy suggestions?	What do you think the future holds for the co-payment? Should it be increased/decreased/abolished?

laphone (Sony IC Recorder ICD-PX240) and a mobile phone device (Samsung Galaxy S6 SM-G920F). Interviews took place in the work-place office of the HCP being interviewed allowing for a quiet and confidential space. Interviews ranged in time from roughly 7 minutes–30 minutes. A field diary was brought to each interview to record noteworthy observations.

The study did not have a target sample size; rather it aimed to recruit participants until data saturation of key themes emerged. During data collection, before considering further participation recruitment, preliminary data analysis was conducted to highlight when researchers were approaching data saturation. In addition, the Francis et al. method was intended to be used to determine data saturation [25]. This method involves identifying an initial analysis sample size and then defining a stopping criterion. The stopping criterion is a defined number of interviews that will take place in which no new themes will emerge. It was agreed that data saturation had been reached after 16 interviews with no new themes emerging in the additional three interviews.

2.3. Analysis

The framework method was used to identify themes emerging from the data obtained and was chosen because of its relevance in policy change and detailed format in comparison to regular thematic analysis [17,26]. The framework method contained seven key stages that allowed for the categorisation and organisation of the large amounts of data to help develop underlying themes and emerging phenomena. These seven stages consisted of i) transcription ii) familiarisation with the interview iii) coding iv) developing a working analytical framework v) applying the analytical framework vi) charting data into the framework matrix and vii) data interpretation and mapping [27,28]. The framework constructed throughout this process was continually amended and "tested for fit". Language was seldom altered in an attempt to retain original meaning and context. The analysis was interpretative recognising the interaction between the researcher and the data.

The data were managed through NVivo12 Plus, QSR International software [29]. Data analysis was conducted by COB, a research pharmacist undertaking a clinical pharmacy PhD. Inter-coder reliability was used at early stages of the project to ensure a high rate of intracoder reliability on subsequent manuscript data analysis. A sample of four random manuscripts were coded and indexed by BOF. At the time of data collection, BOF was an undergraduate pharmacy student. Both COB and BOF discussed arising differences in this process to ameliorate the accuracy of the thematic framework and the application of the framework to sub-

Table 3

Characteristics of interviewees.

Sex	Male	13
	Female	6
Frequency of age groups (years)	25–29	3
	40–44	6
	45–49	4
	50–54	1
	55–59	2
	60–64	0
	65–69	3
Number of years practising	15–19	9
	20–24	5
	25–29	2
	30–34	0
	34–38	1
Employment status	40–44	2
	Full time	14
Year received professional body number	Part time	5
	Pre-1980	3
	1980–1984	1
	1984–1989	0
	1990–1994	3
	1995–1999	8
2000–2004	4	

sequent transcripts. Some disagreements in coding arose. The most common reason for disagreement was redundant labels/codes describing for the same phenomenon e.g., dissatisfaction with Government and anger towards the Irish Health Service Executive (HSE). Through discussion, these indexing discrepancies were resolved [30]. Both COB and BOF had undertaken qualitative data analysis training courses prior to data collection.

2.4. Ethics

Ethical approval was sought from and granted by the Clinical Research Committee of the Cork Teaching Hospitals prior to study commencement. The consolidated criteria for reporting qualitative research (COREQ) statement guided study reporting [31] (see online appendix 4).

3. Results

Nineteen HCPs were interviewed in total each with varying experience (Table 3). The Framework approach produced three main themes where each are elaborated on below. In the reported analysis, participant pseudonyms were created to provide information about: practice ownership (Independent ('Indep') or Franchise

(‘Fran’): community pharmacist participant number (‘CP1’) or general practitioner participant number (‘GP2’).

3.1. The withheld tax-collecting pharmacist

It was unanimously accepted that although the current co-payment system has advantages pertaining to cost containment and waste reduction, the pharmacist is just one party who suffers from its consequences “I didn’t study for five years in order to become an organ of revenue collection for the Government, it is outside the terms and conditions of my role and it’s certainly outside the terms and conditions of my contract with the HSE to raise money for the revenue commissioners” *IndepCP11*. Pharmacists can occasionally find themselves in “dangerous situations” *FranCP12* upon co-payment retrieval, and in scenarios whereby they must supply the medicine without retrieving the co-payment “you’re spending your time trying to look after the best interests of the patient and sometimes the best interests of the patient is I need you to take these medications so I’m going to have to sacrifice. My duty of care to you as a patient trumps my duty of care to the state to collect a tax for them. So therefore the net loser in that transaction is the pharmacist who essentially is now working for free” *IndepCP11*.

Pharmacists also expressed a loss of workplace productivity by collecting the co-payment “if it’s simply that they’re paying by credit card its taking up a minute, two minutes but you add that 100 times a day, your efficiency is gone down dramatically and that’s time that’s taken from something” *IndepCP05*. Pharmacists too experience patient disgruntlement at the point of transaction “I think there is still a lack of understanding that it’s a Government levy as opposed to a personal, pharmacist into-the-pocket levy. That is something that is still an area of confusion, even now” *IndepCP02*. There was an emergent consensus that they should not bear the financial loss if a patient cannot/will not pay. When a pharmacist supplies a medicine to a patient who cannot/will not pay, the primary care reimbursement services (PCRS) still deduct this co-payment tax/levy from the pharmacist. In addition, as there is a maximum monthly co-payment cap for households, if family members are not recognised as one household unit on the electronic PCRS system, the pharmacists bear the financial deficit. As a result, pharmacists have reported large financial losses “Tens of thousands of euro for reasons of non-payment, but also for reasons of families weren’t linked properly on the PCRS database. Those are probably the two most common causes of a deficit in what I should have taken in, what the State deducted from me and what I was able to take in” *IndepCP11*.

Pharmacists note that a proportion of GMS patients acknowledge the value of having the co-payment attached to their medicines “..... they think they’re getting good value for money and that it’s a good thing for the country...” *FranCP13*. However the risk to patient safety which arises from having a co-payment system was recognised by community pharmacists: “From the pharmacy perspective it has introduced extra administrative issues, therefore has caused a danger, in my view, to patient safety because if you are having to talk to Mrs. Murphy about a blasted prescription charge, when you really should be concentrating on the prescription and the dose and the interactions and all of this.....” *IndepCP05*.

3.2. The co-payment system – impact and sustainability

Before the introduction of the co-payment on the GMS, medication stockpiling and wastage was noted as a prominent feature by both pharmacists and GPs. “I did a house call and I asked the lady, Oh, where do you keep your tablets? In under the stairs I removed at least 10 Tesco® plastic shopping bags full of unused medication. They were stockpiled in the thing.... There was bags of them....going back like 10 years..... There was like tens of thousands of tablets that she wasn’t taking” *IndepGP02*. Medication waste seems to be ongoing

but not at the level that it once straddled. “unfortunately, we see it particularly again when patients pass away, the big black bag of unused medication, I don’t believe the black bags have got any smaller since the October 2010, till January 2018” *FranCP08*.

The consensus from interviewees is that the co-payment system influences medicine utilisation and adherence rates. “The *FRN* stuff would be the first to go, so if there are items they genuinely don’t need, they would be the ones that would first go” *IndepCP04*. However, some pharmacists advocate “the co-payment certainly has diminished compliance for certain groups of people. So I think in terms of benefits to how people take their medicine, the people that come back regularly for medication, when there was no 2.50 levy or no 50 cent levy, would generally be compliant. There are people that now choose to come back regularly for certain items and not for others or they will take items, run them up and not take them the next month, so they’ll alternate items, you know. So that certainly isn’t beneficial when a patient has to make a decision as to whether their blood pressure is more important than their cholesterol. You don’t feel your blood pressure being high. You don’t feel your cholesterol level being high. They would be always the easier ones to drop” *FranCP13*. This is worrying as it means patients have to choose between which essential medications to take which poses a big threat to patient safety. This feature is also observed amongst patients without medical cards how much more they pay for medication “..... It’s the poor private paying patient.... They’ll come to you and they’ll say, Look, ok, that blood pressure tablet and it might be for example an ACE inhibitor, what’s the cheapest one I can get of that?” *IndepGP02*.

Most HCPs agree that the co-payment system is a good tool to deter moral hazard but not to generate revenue “if it was 50 cents like it had been initially, then there’s an understanding of why it’s there. Going to 2.50 in 2013 was the one that impacted most..... So, 2.50 would probably be the straw that breaks the camel’s back in terms of the amount that patients are going to pay. Being at the 50 cent charge was the one to leave it at. We understood the policy behind it, you know. Trying to increase it up to generate revenue just doesn’t make sense from a health point of view” *FranCP13*. In fact, HCPs recommend eligible patients with a long-term illness (LTI), as classified by the HSE, to switch to the LTI scheme where there is no co-payment on prescription medicines i.e. GMS co-payment (tax) avoidance “we’ve been migrating them (eligible medical card patients) over to the LTI scheme” *IndepCP02* and “if you go online to the Diabetes Ireland website, they’ll tell you, if you’ve a medical card, make sure you get a long-term illness’. So they’re actually telling people to avoid the levy” *IndepCP11*. However, some participants described the unfairness of this scheme which is not means tested “Why should a long term illness patient, you can have a retired High Court judge, a retired Taoiseach who might have Type 2 diabetes availing of all those levies for their cardiovascular medicines, their statins, their aspirin all free of charge, not even a levy paid and somebody with mental health difficulties who could be in very poor social circumstances, an social welfare, having to pay €2. That is grossly unfair” *IndepCP11*.

Both pharmacists and GPs want the system to remain in place “if Sinn Féin (An Irish left-wing Irish republican political party) get into Government, they might promise to abolish it (the GMS co-payment) as a great stroke to the people, but I firmly believe that the people in the medical card system get an excellent service for nothing and that the co-payment is a very small little contribution to the exchequer and it’s tiny in the overall scheme of things” *IndepGP03*. Notwithstanding this perspective, it was interesting to note that some interviewees suggest that the co-payment system “should be means tested” in order to reduce health inequalities *IndepGP05*. As well as GPs who believe that “GP unions should be involved in co-payment policy because it does affect the workload” *IndepCP01*, pharmacists want to be heavily involved in the co-payment policy. They have many suggestions for co-payment policy improvement

"The fee should certainly be decreased down back to 50 cent, but with a greater emphasis then on exemptions so that there could be specific patients who shouldn't have to pay, a greater cohort of patients that shouldn't have to pay. So say for example, if a patient is diagnosed with cancer and is entitled to a medical card, then they should be getting the medical card and have it free of charge" **FranCP13**.

3.3. Concerns and prescribing patterns of physicians

GPs report that the co-payment has fine-tuned their prescribing habits "has made me a little bit more conscious of what I prescribe for patients in that are they going to take it? Are they going to pay 2.50? Oh, it doesn't sound like a lot, but do you know, whatever it is, it's nearly €30 a year, whatever, per item and patients on a social welfare budget, that's an awful lot of money. So it makes me a little bit more conscious of it" **IndepGP06**. In addition, the co-payment seems to create additional dialogue in the medical surgery "Maybe I get into the conversation of what they need this month more so than I would have in the past" **IndepGP05**. It appears that having a co-payment system on medicines may result in a more customised prescription for the patient.

An unforeseen concept that arose was the potential introduction of a co-payment system attached to GP surgery visits for medical card holders. Medical card holders currently avail of unlimited GP surgery visits free at the point of access. This was first alluded to by a pharmacist in the early stages of data collection phase "...if the patient had a medical card and had to pay €5 to see the doctor or €10 to see the doctor, they'd see something then. ..." **FranCP09**. When interviewing subsequently commenced with GPs, this idea was something that materialised through many indirect quotations where one GP summarised the opinion concisely "I think we are heading towards free GP care and free medication which I don't necessarily agree with.GPs would be in favour of advocating for co-payment both for medication and attendance of surgery visits" **IndepGP06**. As there is an ongoing general practice crisis with over 25 communities without a GP [32], the potential introduction of a co-payment system attached to GP surgery visits for medical card holders could prevent unnecessary consultations thus maximising current GP performance.

4. Discussion

This exploratory study provides a range of insights into HCP views on GMS pharmaceutical policy change over the last decade. What was evident from this analysis is that all participants, in some manner, think the GMS prescription medicine co-payment system is a good idea. However, the pharmacist cohort state they do not want to be an "organ of revenue collection" for the GMS co-payment. This tends to result in various losses of productivity that are not remunerated. Indeed, this financial loss is much more than not being able to retrieve the levy. It is felt in the form of loss of staff productivity where administration workload and procedures have dramatically increased. In addition, it appears that the current information technology (IT) systems are not fit for purpose with respect to GMS co-payment retrieval. Financial losses suffered by pharmacists are also brought about by the absence of family unit linking on IT software systems in the pharmacy setting. For example, one family might pay the GMS co-payment cap of €20 for medicines per calendar month. However, because of poor IT systems communication, it not is recognised that the individuals in the family who form a family unit all fall under the GMS co-payment cap, therefore the PCRS will deduct the €20 co-payment cap for each individual instead of for the family unit per calendar month resulting in financial loss for the pharmacist. This is something which needs to be rectified by the PCRS. From the data,

pharmacists would be happy to be removed from their current role in the co-payment retrieval transaction. As the GMS co-payment is a tax, it could be argued that patients should deal directly with the tax collector/revenue commissioner regarding the payment of this levy as is done with other forms of taxation. Alternatively, pharmacists may be remunerated for co-payment collection, or at the very least, not financially penalised when they are unsuccessful at co-payment retrieval as is currently the case. The literature is sparse on this topic and further research is required.

Like in some Western European countries [33,34], publicly insured patients in Ireland including those aged over 70, those under 6 years and carers avail of GP visits, free at the point of access [13]. An unexpected finding from this study was that GPs have suggested that a similar co-payment policy be attached to GMS patient-physician consultations that occur in their medical surgeries to prevent unnecessary overuse of this free saturated service [32]. This finding indicates that overburdened GPs are aware of the concept of moral hazard and are proposing potential solutions on how to handle increasing demand on healthcare services. More European countries are attempting to or already have put policies like this in place for publically insured patients [34]. For instance, patients aged 20 years or older on the public health insurance scheme in Sweden pay a co-payment of approximately €10 to a front desk receptionist per primary care physician visit [35]. Although subtleties exist across different Swedish regions, in general, the co-payment is seen as an income to the primary care centre, and this will be taken into account when distributing funds from the regional government to each care centre. In the Czech Republic, the evidence reveals no overall effect of doctor visit co-payments on the number of children's doctor visits [36]. However, before such a policy could be implemented in Ireland, the fee for this co-payment would have to be carefully selected. Some research has found that prescription medicine co-payment could potentially affect the number of doctor visits [37] especially higher co-payment fees which may reduce healthcare service utilisation mainly because of a demand reduction of poorer patients [38]. Thus, more in-depth investigation is required to determine the optimal co-payment fee per patient-physician consultation in primary care and how best this fee could be retrieved in practice.

It was unclear to participants what evidence is guiding these GMS co-payment fee changes. GMS co-payment changes are usually announced around general election time by contesting politicians or on national budget day by Government officials, unaccompanied by any solid evidence of what impact such increases or decreases can have. Previous iterations have yielded reductions in adherence to essential medicines, including anti-depressant medications with a large decrease of -10.0% [12]. Reduction in the use of essential medicines results in worsening patient adherence, leading to poorer health outcomes and increased usage of health services [39–41]. This is a healthcare policy not a revenue generating exercise. If Ireland's ten-year Síntecare plan for whole health system reform through political consensus is going to be implemented successfully, then healthcare policymakers need stakeholder buy-in to ameliorate existing pharmaceutical policies like this. In this study, both GP and pharmacy unions have expressed interest to be more involved in the policy formation stages, not the post-implementation stages. Síntecare represents a unique opportunity for all key stakeholders including policymakers, HCPs and patients to collaborate and provide input into a healthcare system that works for all.

It appears that GMS co-payment policy is having a ripple effect on the LTI pharmaceutical policy. HCPs and others have recommended GMS patients with an "eligible" LTI, as classified by the HSE, to avoid paying the co-payment by switching to the non-means tested LTI scheme. Although the dispensing fees paid to community pharmacies for both GMS and LTI reimbursement schemes are

equivalent [7], this switching of schemes creates extra administrative burden elsewhere in the health system. It results in patients straddling two schemes at pharmacy level. Patients get their LTI related medicines free of charge while concomitantly using the GMS scheme to retrieve their non-LTI related medicines. This lead to discussion on the complexity of the whole medicine reimbursement system in Ireland and the associated co-payments where over 20 such schemes exist in the primary, secondary and tertiary care settings [7,42]. One HCP summarised the medicine reimbursement and the GMS co-payment system in Ireland quite nicely "Even saying this out loud sounds absolutely ridiculous, you know, because if you landed from Mars and you said, 'I've got an idea for a tax/co-payment fee', nobody would think that this was credible" *IndepCP11*.

5. Limitations

This study is not without its limitations. Access to the total number of patients that each medical practice serves, and which proportion of those patients were GMS patients, was unattainable. Such information could have been useful in drawing conclusions between the socioeconomic differences of different patient groups. Recruitment of participants was conducted between January 2018 and April 2019. Arguably, the data collection could process could have been quicker but the primary researcher (GOB) was involved in multiple ongoing research projects at the time.

As mentioned in the methods section, an initial core set "convenience sample" was used for data collection. Concerns regarding selection bias in recruitment were mediated by the fact that the sample obtained was representative of the practising HCP population. Pilot interviews were excluded from the data analysis. Although valid interviews, the interviewers felt their interviewing techniques at this early stage may have influenced participants' responses. Securing interviews with GPs proved more difficult than with pharmacists which, resulted in disproportionate numbers between the groups. However, an approximately equal amount of pharmacist quotations and GP quotations are reported in the results section of this paper in an attempt to further minimise selection bias.

The main researcher is a research pharmacist and the second interviewer was a final year pharmacy student at the time of data collection, thus there was a possibility that participants gave socially desirable responses. This bias was difficult to eliminate as the research team felt that by disclosing the researchers' backgrounds to interviewees an element of professionalism could be introduced into the interviews. However given that participants were also HCPs practising much longer than both interviewers, it may be taken that the interviewers established a solid rapport with participants and socially desirable answers did not feature dominantly in the results.

From 1st April 2019, around the same time data collection had ceased, for people aged 70 years and over, the prescription charge decreased to €1.50 per GMS prescription item, up to a maximum of €15 per month per person or family [43]. For people aged under 70 years, the prescription charge remained at €2.00, up to a maximum of €20 per month per person or family. Therefore, it is believed that this co-payment change did not affect the study results. Furthermore, in October 2019, the Department of Finance announced that a €0.50 reduction per GMS prescription item for all medical card holders will come into effect in July 2020 [44]. This research was originally intended to be part of a mixed methods study where the overall aim was to determine the impact of altering prescription charges on patient adherence to medicines on the public GMS scheme in Ireland. The quantitative study planned to measure changes in adherence in essential and less-essential medicines [45,46] pre and post GMS co-payment changes. How-

ever, access to national PCRS data [47] required for said analysis is only available to select research institutions.

6. Conclusion

The GMS co-payment has undergone many various iterations in recent times. Previous studies have examined its impact and sought to retrieve "the optimal co-payment" which prevents medicine wastage and acts as a revenue stream [8,12]. However, this study too implies that there is no optimal co-payment fee considered by patients and by HCPs. GPs and pharmacists did seem to favour a lower amount. Perhaps healthcare policymakers should formally evaluate its value every few years to see if change is warranted. The Czech Republic lead by example in this field as they seem to monitor and update their co-payment system quite regularly. Indeed, this study comes at an important time as the Irish Healthcare system undergoes major political, economic and health policy reform under the *Sláintecare* policy [14]. Through political concord, the Irish Government are aiming to reorient the health system 'towards integrated primary and community care, consistent with the highest quality of patient safety in as short a time-frame as possible' [48,49]. This study has provided a platform for experienced primary care HCPs to express their views and accounts of the Irish GMS co-payment system. For the most part, HCPs agree that there is merit to having a nominal charge attached to prescription medicines on the GMS scheme. However, participants have highlighted outstanding issues that need to be optimised to ameliorate primary healthcare practices and procedures [50,51]. With respect to Lewin's basic change theory model of unfreezing, changing, and refreezing [52], healthcare policymakers implementing the ten-year *Sláintecare* reform can bypass the unfreezing stage of this contemporary pharmaceutical policy. Both pharmacy and general practitioner representative bodies want to be involved to support evidence-based policy decisions.

Funding

This research project was funded by Irish Research Council (GOIPG/2016/635). The funders had no part in the design of the study; the collection, analysis, and interpretation of the data; the writing of the report; or the decision to submit the article for publication.

Ethical approval

Ethical approval was sought from and granted by the Clinical Research Committee of the Cork Teaching Hospitals prior to study commencement.

Informed consent

Written and verbal consent was sought and obtained from each participant.

Data availability statement

The dataset used and analysed during the study is available from the corresponding author upon reasonable request.

Author contributions

Gary L O'Brien (GOB), Sarah-Jo Sinnott (SJS), Stephen Byrne (SB), Bridget O'Flynn (BOF), Valerie Walsh (VW), and Mark Mulcahy (MM): GOB, SJS and SB conceived the study idea. GOB, SJS and SB decided on sampling techniques. SB and GOB sought and gained

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8.17 Appendix XVII - Chapter 6 Participant information letter

A qualitative analysis of the healthcare professional stakeholder involvement in pharmaceutical policy change in Ireland

You are being invited to take part in a research project that is being conducted at the University College X.

Before you decide whether or not you wish to participate you should read the information provided below carefully, and you are free to discuss it with your family, friends or colleagues. You should clearly understand the risks and benefits of participating in this study so that you can make a decision that is right for you. Take time to ask questions – do not feel rushed or under any obligation to make a hasty judgment.

You have the right to withdraw your participation at any time (before, during and after the study) for whatever reason without having to justify your decision and with no negative impact for you. Your data will then be excluded from the study results.

Why is this study conducted?

Co-payment policies on the General Medical Services (GMS) scheme have existed since 2010 and have gone through multiple iterations, starting at €0.50 in October 2010 and reduced to €2 in January 2018. The involvement of the Healthcare Professionals (HCPs) such as General Practitioners (GPs) and Pharmacists in such pharmaceutical policy changes on the GMS scheme has not been evaluated. As part of his PhD, X wants to gather feedback on the perceptions and challenges experienced by HCPs resulting from the GMS co-payment changes. For example, are co-payment changes creating additional administrative burden for HCPs? Have altering co-payments influenced GPs' prescribing patterns? How have pharmacists handled the implementation of this policy? What happens if patients cannot afford these prescription medicine co-payments? This study seeks to retrieve qualitative data on HCP stakeholder involvement for all existing co-payment alterations in the Irish context.

Why have you been asked to participate?

You have been asked because you are a Healthcare Professional currently working in a GP practice or a community pharmacy in the Republic of Ireland.

What will your participation involve?

Your participation will involve a 30-minute (maximum) interview about matters relating to your experiences of the effects of the altering GMS prescription co-payments on patients. X, who is a pharmacist, will ask questions as the session progress. A small amount of extra time will be allowed for explaining the aims of the study and your questions about the study.

Will your participation be kept confidential?

Yes, all information will be treated in a confidential manner and your participation is anonymous. The interview will be audio recorded so that it can be transcribed afterwards. Your name will not be recorded on any information which is collected about you. Instead you will be provided with a unique code. The only person with access to the code will be X. The results of the study will be included in X's PhD thesis but there will be no way of identifying you from these results. The results will be seen by X's supervisors, a second marker and an external examiner, again these will be anonymous. The thesis may be read by future students. The study may be presented at scientific conferences and/or published in an academic journal.

The audio recording will be erased once the interview has been transcribed. Transcripts will be stored in a protected manner for 5 years, after which they will be destroyed in line with University College X confidential waste destruction guidelines.

What are the possible benefits of participating?

Your contribution to this study will be used to reveal how HCPs have previously dealt and are currently dealing with these GMS co-payment policy changes since its inception in 2010. X hopes to publish such findings that may influence future healthcare policymaking decisions to the benefit of the HCP and patient.

Are there any risks of participation?

We do not think that participation in this study will have any negative effect on you.

Further information

Approval has been granted to do this study by the Clinical Research Ethics Committee of the Cork Teaching Hospitals.

If you would like a copy of the results, please let X know.

If you need any further information, do not hesitate to contact the primary researcher, X, by telephone X or by email to X or email the supervisor of the project, Professor Y by Y (Telephone:Y).

Thank you for taking the time to read this information sheet. If you agree to take part in the study, please sign the consent form overleaf.

Kind regards,

X

Research Pharmacist, PhD student

8.18 Appendix XVIII - Chapter 6 Participant consent form

A qualitative analysis of the healthcare professional stakeholder involvement in pharmaceutical policy change in Ireland

I _____ declare that information about this research project has been given to me and that I understand the purpose, methods, risk and benefits of participating in this study.

I am aware that participating is voluntary and that I can withdraw my participation at any time with no negative impact on my professional status.

I give permission for my responses in the interview to be audio-recorded and that anonymity will be ensured by disguising my identity.

I understand that disguised extracts from what I say may be quoted in the thesis and any subsequent publications.

I agree that I have received a copy of this Consent Form and a copy of the Information Letter.

I hereby give my informed consent to participate in the research study.

Participant Signature

Date

Would you like a copy of the Interview Transcript?

YES NO

Would you like a copy of the findings after the study is completed?

YES NO

Email address: _____

8.19 Appendix XIX - Chapter 6 Topic guides

Pharmacist Topic Guide

Interviewing practising Irish primary healthcare professionals about their opinions, perceptions, challenges and experience of the GMS co-payment from inception to current day.

Before we start, I just want to check that you are still happy for this interview to be recorded and that you know we can stop at any time.

I would like to thank you for agreeing to participate in this interview and stress that everything said here today is completely confidential. Your name will not appear on any documents or recording discs and I personally will anonymise the transcript from this interview and will ensure that no one else will be identifiable either.

These interviews are part of a study I am conducting for my PhD. The aim of the study is to gain an understanding of the perceptions and challenges experienced by healthcare professionals from the various GMS co-payment iterations since 2010.

There are no right or no wrong answers to these questions.

The interview will probably last between 10-30 minutes.

Does all that sound ok? Are you happy for me to record the interview?

Demographics

- Age?
- Address of Pharmacy? Independent or Franchise Pharmacy?
- Gender?
- Number of years practising in community Pharmacy?
- Full-time/Part-time?
- Year received pharmaceutical society of Ireland (PSI) number?
- Do you have any obvious biases to declare on this topic?

In Supplementary Material **Figure 1** presented to you in the information leaflet, you can see the GMS co-payment has undergone various iterations since its initial introduction in 2010. As you have been practising throughout these changes, I am interested to learn about your experiences in considering these policy changes in your routine clinical practice.

Version 4

1) What are your own thoughts on the GMS co-payment attached to prescription medicines?

- Positive aspects/negative aspects?
- Do you know why it was initially brought in and its impact to date?
- Are you aware of the GMS co-payment exemptions for specific patient groups?

2) How have co-payments influenced your practice and procedures in the Pharmacy, if at all?

- Have they changed the way you and the Pharmacy staff work, if so, how?

- 3) How easy or difficult is it to retrieve co-payments from patients?
- What happens if a patient cannot pay? Do you supply the medicine anyway?
 - Have you a procedure in place for patients who cannot pay?
 - Have you encountered awkward situations when a patient cannot pay?
 - Have you suffered financial loss because of patients not paying?
- 4) In your opinion, have co-payments presented an administrative burden to you/your practice?
- Have you noticed/recommended eligible patients to switch to the long-term illness (LTI) scheme to avoid paying the co-payment?
- 5) How do you think GMS patients perceive paying the co-payment attached to their prescription medicines?
- Do you think the co-payments are reasonably or unfairly priced for GMS patients?
- 6) Do you think co-payments have influenced patients' utilisation of medicines?
- Increase/decrease in patients picking up their medicines?
 - Are there particular types of medicines affected more by the GMS co-payment changes?
- 7) Looking at **Figure 1**, would you have regarded any one of these GMS co-payment changes to be more influential or impactful than the others?
- Effect on patient picking up medication
 - More difficult to retrieve the co-payment from the patient upon being increased?
- 8) Have you noticed any changes to the prescribing patterns of physicians since the introduction and changes in the GMS co-payment?
- Any issues/concerns arising from GPs concerning GMS co-payments?
 - An increase in generic prescribing since the beginning of the co-payment?
- 9) What do you think the future holds for the GMS co-payment?
- Should the co-payment be increased, decreased or abolished?
 - Do you think the previous GMS co-payment changes were evidence-based?
 - How should Pharmacists/representative bodies be involved in this policy, if it all?

Have you anything else to say/add on this topic? Thank you for your time

General Practitioner (GP) Topic Guide

Interviewing practising Irish primary healthcare professionals about their opinions, perceptions and experience of the GMS co-payment from inception to current day

Before we start, I just want to check that you are still happy for this interview to be recorded and that you know we can stop at any time.

I would like to thank you for agreeing to participate in this interview and stress that everything said here today is completely confidential. Your name will not appear on any

documents or recording discs and I personally will anonymise the transcript from this interview and will ensure that no one else will be identifiable either.

There will not be any consequences to what you tell me and there will be no blame attributed to you or anyone else.

These interviews are part of my PhD There are no right or no wrong answers to these questions, just give as much detail as you can. It will probably last between 10-30 minutes. Does all that sound ok? Are you happy for me to record the interview?

Demographics

- Age?
- Address of GP practice? Independent or medical centre practice?
- Gender?
- Number of years practising as a GP?
- Full-time/Part-time?
- Year received Irish medical council (IMC) number?
- Do you have any obvious biases to declare on this topic?

In Supplementary Material **Figure 1** presented to you in the information leaflet, you can see the GMS co-payment has undergone various iterations since its initial introduction in 2010. As you have been practising throughout these changes, please answer the following questions with respect to this.

Version 2

- 1) What are your own thoughts on the GMS prescription medicine co-payments?
 - Positive aspects/negative aspects?
 - Do you know why it was initially brought in and its impact to date?
 - Are you aware of the GMS co-payment exemptions for specific patient groups? Which ones?
- 2) How have co-payments influenced your practice and procedures as a GP, if at all?
 - Have they changed the way you prescribe, if so, how?
 - Have they influenced the amount of prescriptions you issue, if so, how?
 - What happens if you know a patient cannot pay? Do you still prescribe the medicine?
 - Have you noticed/recommended eligible patients to switch to the long-term illness (LTI) scheme to avoid paying the GMS co-payment?
- 3) How do you think GMS patients perceive paying the co-payment attached to their prescription medicines?
 - Do you think the co-payments are reasonably or unfairly priced for GMS patients?
- 4) In your opinion, are GMS co-payments effective at preventing patients from collecting medicines they actually do not require?
 - Yes/no – Why?
- 5) In what way, if any, do you think co-payments have influenced patients' utilisation of medicines?

- An increase in patients asking you to prescribe/deprescribe certain medicines
- A decrease in patients asking you to prescribe/deprescribe certain medicines

6) In your opinion, are there particular types of medicines affected more by the GMS co-payment changes?

7) Looking at **Figure 1**, would you have regarded any one of these GMS co-payment changes to be more influential or impactful than the others?

- Effect of patient asking you to prescribe/deprescribe certain medicines
- Patient expressing concern to you on co-payment changes

8) Have you encountered any issues or concerns from patients concerning GMS co-payments that they may have experienced when collecting prescription medicines at their pharmacy?

9) Have you encountered any issues or concerns from pharmacists concerning GMS co-payments that they may have experienced when serving patients in the pharmacy?

10) What do you think the future holds for the GMS co-payment?

- Should it be increased, decreased or abolished?
- Do you think the previous GMS co-payment changes were evidence-based?
- What advice have you for policymakers on it? Should GP representative bodies be involved?

Have you anything else to say/add on this topic? Thank you for your time



Figure 1 | Timeline review of recent GMS co-payment introductions and changes 2010-2018

8.20 Appendix XX - Chapter 6 COREQ checklist

Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist (370)

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

YOU MUST PROVIDE A RESPONSE FOR ALL ITEMS. ENTER N/A IF NOT APPLICABLE

No. Item	Guide questions/description	Response
Domain 1: Research team and reflexivity		
<i>Personal Characteristics</i>		
1. Interviewer/facilitator	Which author/s conducted the interview or focus group?	GOB and BOF
2. Credentials	What were the researcher's credentials? E.g. PhD, MD	GOB (BPharm, MPharm, PhD Student)
3. Occupation	What was their occupation at the time of the study?	PhD Student/Research Pharmacist
4. Gender	Was the researcher male or female?	Male
5. Experience and training	What experience or training did the researcher have?	Short Course in Qualitative Research Methods, Health Experience Research Group, May 2018, University of Oxford
<i>Relationship with participants</i>		
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	Based on participant information letter provided
8. Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	Minor characteristics included in participant information letter provided
Domain 2: study design		
<i>Theoretical framework</i>		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	Framework approach/ Framework analysis
<i>Participant selection</i>		

No. Item	Guide questions/description	Response
10. Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball	Purposive sampling followed by snowballing
11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	Email, phone, face-to-face
12. Sample size	How many participants were in the study?	19
13. Non-participation	How many people refused to participate or dropped out? Reasons?	0
<i>Setting</i>		
14. Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	Respective interviewee's workplace
15. Presence of non-participants	Was anyone else present besides the participants and researchers?	No
16. Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	Healthcare professional practising before the introduction of the co-payment in 2010 to end of study date
<i>Data collection</i>		
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Questions were based on the topic guides used
18. Repeat interviews	Were repeat interviews carried out? If yes, how many?	N/A
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	Two methods of audio recording were used – Dictaphone and mobile phone devices
20. Field notes	Were field notes made during and/or after the interview or focus group?	Notes were added to a field diary immediately after the interview
21. Duration	What was the duration of the interviews or focus group?	7 - 30 minutes
22. Data saturation	Was data saturation discussed?	Yes (Francis method(365))
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	Optional if participants required – choice presented on the consent form
Domain 3: analysis and findings		
<i>Data analysis</i>		

No. Item	Guide questions/description	Response
24. Number of data coders	How many data coders coded the data?	One primary coder (GOB) where one co-author (BOF) performed data verification (intercoder reliability)
25. Description of the coding tree	Did authors provide a description of the coding tree?	Yes
26. Derivation of themes	Were themes identified in advance or derived from the data?	Both deductive and inductive themes are presented
27. Software	What software, if applicable, was used to manage the data?	NVivo 12 Plus - QSR International
28. Participant checking	Did participants provide feedback on the findings?	No
<i>Reporting</i>		
29. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	Yes
30. Data and findings consistent	Was there consistency between the data presented and the findings?	Yes
31. Clarity of major themes	Were major themes clearly presented in the findings?	Yes
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Yes

8.21 Appendix XXI - Chapter 6 Ethical approval



Coláiste na hOllscoile Corcaigh
University College Cork, Ireland

An Coláiste Leighis agus Sláinte
College of Medicine and Health

Scoil na Cógaíochta
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www.ucc.ie/pharmacy

Prof Molloy, (Chairman)
Clinical Research Ethics Committee of The Cork Teaching Hospitals
c/o Secretariat,
Lancaster Hall,
6 Little Hanover Street,
Cork.

17th October 2017

Dear Prof Molloy,

Attached please find enclosed for the following approved study:
Patients' opinions of generic substitution and reference pricing changes within the Irish Healthcare Sector (Ref ECM 3(e) 04/02/14)

1. Annual Protocol Renewal Survey including a study summary to date.
2. A study Amendment Application form for the same study.

I request that the Ethics Committee review this research project through an expedited review procedure as it involves the study of existing data and documents.

I hope that all the relevant information has been supplied, but please feel free to contact me should any further details be required.

Thanking you in advance,

Yours sincerely,

Prof Stephen Byrne
BSc Pharm. (Hons) PhD
Chair of Clinical Pharmacy Practice &
Head of School
School of Pharmacy
University College Cork
Tel. + 353 21 4901658
email: stephen.byrne@ucc.ie

Ollscoil na hÉireann, Corcaigh
National University of Ireland, Cork

Clinical Research Ethics Committee Of The Cork Teaching Hospitals

ANNUAL PROTOCOL RENEWAL SURVEY

*PLEASE SEND TO CREC ANNUALLY FROM DATE OF ORIGINAL APPROVAL
Failure to submit an annual report will necessitate termination of the research.*

Name of Chief Investigator: Prof Stephen Byrne
Department/Hospital: Professor of Clinical Pharmacy Practice and Head of School,
School of Pharmacy
Address: School of Pharmacy, University College Cork, Cavanagh
Pharmacy Building, College Road, Cork

Study title: Patients' opinions of generic substitution and reference pricing changes within the Irish Healthcare Sector (Ref ECM 3(e) 04/02/14)
Type of Study: Qualitative interviews
Organ System: NA
Disorder: NA
Drug or Device: NA
Special Populations: NA
Number of subjects recruited to date? 20

Answer Yes or No to the following:

Has the Study been terminated?	No
Has an End of Trial Declaration Form been submitted to CREC?	No
Has this study been changed in the past 12 months?	No
Have these changes been approved by the CREC?	NA
Has any subjects on this study suffered an adverse reaction in the past 12 month?	NA
If yes, have these adverse reactions been reported to the CREC?	

Does this study involve the use of investigational drugs or devices?

NA

If yes, name the Investigational drug or device used in this study

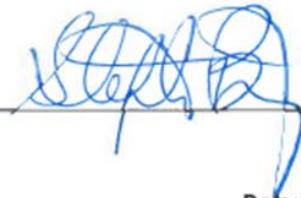
Will further subjects be enrolled into this study?
If not sure, indicate yes.

YES

Was Informed Consent obtained?

YES

Chief Investigator Signature: _____



Date: _____

17/10/17

Chairman Signature: _____

Date: _____

Clinical Research Ethics Committee Of The Cork Teaching Hospitals

AMENDMENT APPLICATION FORM

See Page 7 for list of documents required.

Please note that submission of an incomplete application pack will result in the application being returned to the study Chief Investigator. The application will not be reviewed.

The study title on this amendment application form must be exactly the same as the title on the original application.

Chief Investigator Details

Name of Chief Investigator: Prof Stephen Byrne

Hospital and Department: School of Pharmacy, University College Cork, Ireland

Study Title: Patients' opinions of generic substitution and reference pricing changes within the Irish Healthcare Sector (Ref ECM 3(e) 04/02/14)

The following changes are proposed for the study:

Answer Yes or No to the following:

Chief Investigator: No

Co-investigator(s): Yes, I would like to add the following final year project student Bridget O'Flynn and the following PhD research Pharmacist, Mr Gary O'Brien.

Dosage: No.

Treatment Procedures: No.

Drug/Device: No.

Study Population: No.

Number of Subjects: To increase from 20 to 40 subjects.

Risks: No additional risks

Answer Yes or No to the following:

Is a revised study protocol necessary as a result of this amendment? **No**
If yes, please attach a revised protocol to this amendment.

Is a revised Participant Information Leaflet and Consent Form necessary as a result of this amendment? **No**
If yes, please attach a revised consent form to this amendment.

Please list the specific changes from the previously approved protocol and provide sufficient rationale for each change to allow the committee to make a decision.

The specific change is to co-investigator, i.e. I would like to add the following final year project student Bridget O'Flynn and the following PhD research Pharmacist, Mr Gary O'Brien.

Chief Investigator Signature: 

Date: 17/10/17

(This form must bear the original signature of the Chief Investigator)

Post Application to: Lancaster Hall, 6 Little Hanover Street, Cork

An Evaluation of Patients' Opinions and Perceptions of Generic Substitution and Reference Pricing

Introduction:

The Health Services in Ireland introduced generic substitution and reference pricing as cost containment measures in June 2013. Limited research of Irish patients' opinions and perceptions of these policies has been carried out to date. Therefore, the aim of the study was to analyse patients' opinions and perceptions of generic substitution and reference pricing.

Methods:

A qualitative research design was employed by carrying out twenty semi-structured interviews in eight community pharmacies; thirteen females and seven male patients were interviewed. Ten were eligible for the General Medical Services Scheme (free healthcare). Recruitment took place in independent and multiple pharmacies in rural and urban settings. Thematic content analysis was conducted using QSR International's NVivo (ver. 10). The "Francis Method" was used to test for data saturation.

Results:

Results show a generally positive opinion of generic substitution and referencing pricing but there was limited patient awareness, especially in relation to referencing pricing. Willingness to accept generics was often linked to recommendations by the pharmacist and doctor. Sceptical patients feared the quality, safety and efficacy of generic medications as well as reporting factors such as older age and disturbing routine as possibly affecting medication adherence. Personal experience was recognised as shaping many patient views in addition to affordability issues and opinions on co-payments.

Conclusion:

This study gives an insight into patients' level of knowledge and understanding of generic substitution and reference pricing. Educational measures to enhance acceptance and ensure success of these policies have been highlighted by patients in this study.



UCC

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COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee

Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

Our ref: ECM 4 (j) 07/01/14 & ECM 3 (u) 07/11/17

26th October 2017

Professor Stephen Byrne
School of Pharmacy
Cavanagh Pharmacy Building
College Road
Cork

Re: Patients' opinions of generic substitution and reference pricing changes within the Irish Healthcare Sector.

Dear Professor Byrne

The Chairman approved the following:

- Cover Letter dated 17th October 2017
- Annual Progress Renewal Survey signed 17th October 2017
- Amendment Application Form signed 17th October 2017
- Addition of Bridget O'Flynn, Final Year Student and Gary O'Brien, PhD Research Pharmacist.

Approval is granted to implement this amendment.

Please keep a copy of this signed approval letter in your study master file for audit purposes.

You should note that ethical approval will lapse if you do not adhere to the following conditions:

1. Submission of an Annual Progress Report/Annual Renewal Survey (due annually from the date of this approval letter)
2. Report unexpected adverse events, serious adverse events or any event that may affect ethical acceptability of the study
3. Submit any change to study documentation (minor or major) to CREC for review and approval. Amendments must be submitted on an amendment application form and revised study documents must clearly highlight the changes and contain a new version number and date. Amendments cannot be implemented without written approval from CREC.
4. Notify CREC of discontinuation of the study

Submit an End of Trial Declaration Form and Final Study Report/Study Synopsis when the study has been completed

Yours sincerely

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

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

Ollscoil na hÉireann, Corcaigh - National University of Ireland, Cork

8.22 Appendix XXII - Chapter 7 Policy brief

The Health Policy Triangle Framework - Health Policy Analysis and Sláintecare Reform

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Date of issue: September 2020

Issue

The burgeoning literature of health policy analysis sees novel policy frameworks and theories being developed quite frequently. While it is great to observe such advancements in the field, having too many choices of frameworks and theories can potentially complicate the selection process and hinder their application.

Policy implications

In May 2017, an Irish cross-party parliamentary committee published the '*Houses of the Oireachtas Committee on the Future of Healthcare Sláintecare report*'. Sláintecare sets out a high-level policy road map roadmap to deliver whole system reform and universal healthcare, phased over a ten-year period. Sláintecare details reform proposals which, if delivered, will establish; a universal, single-tier health service where patients are treated solely on the basis of health need; the reorientation of the health system '*towards integrated primary and community care, consistent with the highest quality of patient safety in as short a time-frame as possible*'. Given that Sláintecare implementation is in its early stages, it is argued that incorporation and use of a common descriptive health policy framework should be used in the analysis of all upcoming Sláintecare-related health policy decisions.

Key findings

Using diverse healthcare settings within the Irish context, researchers from the Irish Health Service Executive, London School of Hygiene & Tropical Medicine, and University College Cork have recently analysed local, regional and national healthcare policy change over the last decade with regard to (1) development processes, (2) evidence generation, (3) implementation, and (4) outcomes using the health policy triangle (HPT) framework. The research trialled the generalisable nature of the HPT framework when applied to various health-related policy decisions at different stages in their life cycle and subsequently proved it can be used at local, regional and national level. The HPT framework helped describe:

- A policy decision concerning the initiation and switching of patients to biosimilar infliximab CT-P13 from the originator medicinal product at local level. It was decided to conduct a literature review on the supporting evidence behind this policy decision. The HPT framework was applied as a scaffolding framework to describe the various contributing components which ultimately led to the successful implementation of the biosimilar policy.
- A policy decision concerning whether a physician would be the most cost-effective healthcare professional to implement a medication screening tool based upon the STOPP/START criteria from the perspective of the Irish health service at local level. A cost-effectiveness analysis alongside conventional outcome analysis in a cluster RCT

was used to generate compelling evidence. The HPT framework was used to describe the different relevant components which show how this contemporary policy is still evolving.

- A policy decision concerning whether trastuzumab subcutaneous treatment should replace trastuzumab intravenous treatment for HER2-positive breast cancer patients in routine clinical practice at regional level. A prospective observational study in the form of cost minimisation analysis constituted study design and was used to produce credible evidence to support policy change. The HPT framework was used to describe the various contributing components which show how this topical policy is still maturing.
- A pharmaceutical policy concerning the mandatory co-payment fees attached to prescription medicines on the national Irish public health insurance scheme. It was unknown what impact these changes have on relevant stakeholders who work at the coalface of this labile policy. A qualitative study using purposive sampling alongside snowballing recruitment was used to generate compelling evidence. The HPT framework was used to depict the interrelated factors which underpin this national pharmaceutical policy.

Recommendation

This research has illustrated how generalisable and adaptable the HPT framework is when applied to health-related policy decisions in various Irish healthcare settings. Given this advantage, it is proposed that the HPT framework should be used in Sláintecare reform policy. Using a common descriptive framework and standardising the approach to health policy analysis during this ten-year reform has the potential to increase the successful fruition of Sláintecare policy goals.

Further reading

O'Brien GL., Using the Health Policy Triangle Framework to Describe Local, Regional and National Healthcare Policy Changes within Ireland's Diverse Healthcare Settings, PhD Thesis. <https://cora.ucc.ie/handle/xxxxxx> (in press)