A Research Programme to Model, Establish and Evaluate Testing and Treatment of Hepatitis C Infection in Community Pharmacy

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DECLARATION

This dissertation is the result of my own work and includes nothing, which is the outcome of work done in collaboration except where specifically indicated in the text. It has not been previously submitted, in part or whole, to any university of institution for any degree, diploma, or other qualification.

In accordance with the Faculty of Health Sciences and Sport guidelines, this thesis is does not exceed 80,000 words, and it contains less than 150 figures.

Signed: 

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ABSTRACT

This thesis aims to present the case for establishing a routine service for testing and treatment of hepatitis C (HCV) for people prescribed opioid substitution therapy (OST) and attending community pharmacies. In order to support its contention, it reports on the methodological strategies, knowledge translation and evidence outcomes from the contributions of a series of published research studies. The studies were the outputs from a research fellowship provided by Gilead and from two research grants obtained from Gilead, the Scottish Government and Bristol Myers Squibb during the period 2013-2018. The studies were conceptualised, developed and interpreted through participatory and iterative research planning processes. The research drew on theories and constructs from many sources, but was especially reliant on the Medical Research Council's Framework for the development and evaluation of complex interventions to improve public health. Its key generalisable findings are summarised as follows:

-The identification of a large, but fragmented pool of knowledge indicating that the technology provided through innovation in medicines design and marketing can lead to a simplification of healthcare processes and therefore increase access for vulnerable and stigmatised populations

-That the way healthcare is organised may be determined by inertia and the needs of health services, rather than by the effective deployment of resources to maximally impact on health gain

-The implementation of innovative services in healthcare requires additional skills to those established and recognised as central to development of evidence-based healthcare. These include practical approaches to stakeholder management, resource deployment and contracting. The political context and business objectives of stakeholders may have greater weight in determining uptake of a service than evidence of population health gain.

-That the real life healthcare environment can provide the context for healthcare research and evaluation and that the participation in research by stakeholders, service providers and patients can be part of the process of modernisation of heath care services.

This thesis aims to establish the case that the programme of research presented has made an original and useful contribution to knowledge on design, implementation and evaluation of a community pharmacy service. It further aims to build the case that evidence generated in this

way can inform and support policy development in the wider context, with a reappraisal of capability and capacity.

Its most significant contributions have been:

-Support for the delivery of the WHO strategic aim for the Elimination for Hepatitis C as a public health concern by 2034.

-Providing supporting evidence and guiding the development of recommendations

-Informing and supporting the development of Governments' policy on elimination of hepatitis C as a public health concern

ACKNOWLEDGEMENTS

I have loved being a pharmacist and practising my profession. At 16 years old I first started working in the local pharmacy operated by an Independent contractor, Mr Keith Berridge, who fascinated me with the way medicines were used and how people sought advice about uncertainties with their health, from a shop on the high street. My undergraduate degree at University of Bradford, led to a training post in North Staffordshire, where I saw pharmacists working in clinic alongside physicians, using their skills to manage anticoagulated patients. My first job after joining the Pharmacy Register was as a Resident Pharmacist for Peter Taylor at Airedale Hospital, where I spend my entire day (and many evenings and weekends) working alongside clinicians in a ward environment and contributing to the care of patients. As a Teacher-Practitioner in Sunderland, I got my first chance to initiate and evaluate pharmacy services and to choose how to deploy resources to improve health. The kindness of John Hall, my friend and colleague stays with me to this day.

The journey that has led me to undertaking this PhD has been the course of my career. I am grateful to Brian Williams for encouraging me to formalise my efforts at service innovation into a programme of study and to Linda Bauld for knowing just what I required before I did. I thank Josie Evans for helping me to navigate the governance of university regulations and providing encouragement. I particularly acknowledge and thank John Dillon, whose leadership of the efforts to eliminate Hepatitis C in Scotland have been the context and rubric for my programme of study. I have been fortunate indeed to be able to work with him and the team at NHS Tayside. I thank Drew Walker for giving me the space to undertake research as part of my role as a Consultant in Public Health within a supportive environment.

The results presented in this thesis are the research outcomes of research grants from a range of funders, especially Gilead but also the Scottish Government and Bristol Myers Squibb. The research questions addressed attempt to demonstrate a robust pathway to establishing an evidence-based community pharmacy care pathway. This work forms a small part of the much wider effort to remove an avoidable mortal disease from a vulnerable population experiencing profound health inequalities.

Finally I would like to record my appreciation of my family's support. My wife Sheila has provided the emotional, intellectual and practical encouragement I required and has been relied upon, much more than I have said.

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CHAPTER 1

INTRODUCTION: THE CASE FOR MODELLING, ESTABLISHING AND EVALUATING TESTING AND TREATING HEPATITIS C IN COMMUNITY PHARMACY

In May 2016, The World Health Assembly adopted the first "***Global Health Sector Strategy on Viral Hepatitis, 2016-2021***". The strategy highlights the critical role of Universal Health Coverage and the targets of the strategy are aligned with those of the Sustainable Development Goals. The strategy has a vision of eliminating viral hepatitis as a public health concern and this is encapsulated in the global targets of reducing new viral hepatitis infections by 90% and reducing deaths due to viral hepatitis by 65% by 2030. (WHO 2016)

"Viral hepatitis is an international public health challenge, comparable to other major communicable diseases, including HIV, tuberculosis and malaria. Despite the significant burden it places on communities across all global regions, hepatitis has been largely ignored as a health and development priority until recently. It will no longer remain hidden, however, with the adoption of the resolution on the 2030 Agenda for Sustainable Development".

Content

This chapter is an introduction to thesis contents. It provides an overview of the knowledge and evidence that guided and shaped the aims and rationale for the research presented in this theses, culminating in delivery of the SuperDOT-C cluster randomised trial.

1.1 Thesis aims and objectives

This thesis aims to make a useful and original contribution to the evidence base guiding the global response to the elimination of hepatitis C (HCV) as a public health concern. It also aims to demonstrate the knowledge translation contributions of its research outcomes to policy development processes.

The primary purpose of all research presented in this thesis has been to support the development of more effective care pathways that enable greater access to testing and treatment of hepatitis, by the disadvantaged and vulnerable populations who are prescribed opioid substitution therapy (OST) to treat their injecting drug use. In the United Kingdom, the practical delivery of OST is mainly undertaken by community pharmacists.

The "***Global Health Sector Strategy on Viral Hepatitis, 2016-2021***" (WHO 2016a) sets out five strategic directions that it suggests are vital to the elimination of viral hepatitis as a public health threat:

Strategic Direction 1 Information for focused action:	Developing a strong strategic information system to understand viral hepatitis epidemics and focus the response;
Strategic Direction 2 Interventions for impact:	Defining essential, high-impact interventions on the continuum of hepatitis services that should be included in health benefit packages;
Strategic Direction 3 Delivering for equity:	Strengthening health and community systems to deliver high-quality services to achieve equitable coverage and maximum impact;
Strategic Direction 4 Financing for sustainability:	Proposing strategies to reduce costs, improve efficiencies and minimise the risk of financial hardship for those requiring the services;
Strategic Direction 5 Innovation for acceleration:	Promoting and embracing innovation to drive rapid progress.

Within the context of these broad strategic goals, the specific aim of this thesis is to present evidence on how the community pharmacy health-promotion resource can be wielded to deliver an innovative and effective contribution to the health sector response to the Strategy.

Objectives and Goals

The purpose of this research is to explore a range of patient outcomes associated with a change in delivery model from a current hospital-based pathway to a primary care-based pathway delivered through community pharmacy.

Although the clinical trials used to enable licensing of the medicines to treat HCV infection demonstrate safety, quality and efficacy of direct acting antiviral medicines (DAAs), the effective delivery of a new care pathway in a real-world environment and within the context of the day-to-day life of a vulnerable population is not described for a community pharmacist-led intervention.

The way that the National Health Service operationalises clinical trials evidence is of general concern (Glasziou and Haynes 2005). Standard evidence used to satisfy regulatory bodies does not address the interactions between people who use a service, the staff that provide the services and influence of the environment within the community at large. These interactions may produce different results to those described within a clinical trial.

Programme Research Questions

Can a pharmacist-led care pathway designed to test and treat HCV infection in people prescribed OST, increase the numbers of this population who access treatment and cure for hepatitis C?

Secondary Questions

What are the views and experiences of people who access pharmacy services to receive OST?

What are the important factors to be considered in the design of a pharmacist-led care pathway, from the perspective of the service-user population?

Can a pharmacy-based testing service for HCV infection encourage the target population of OST service users to take a test for blood borne viruses (BBVs)?

Is the delivery of a pharmacist-led pathway to deliver testing and treatment for HCV feasible? How do service providers describe the provision of this service?

What are the barriers and facilitators identified that impinge on the access and delivery of effective care?

What are the potential causal mechanisms which may be identified that impinge on access and delivery of effective HCV care?

1.2 Rationale for research aims and objectives

The thesis title describes the desire to establish a care pathway for delivery of testing and treatment of HCV and then to evaluate the effects of this change to health service delivery. The rationale for doing so is to enable a greater number of the people who inject drugs (PWIDs) and are prescribed OST to access the health technologies that will cure them of HCV. The PWID population are a vulnerable group at significant risk of adverse health outcomes and health inequalities.

Randomised controlled trials (RCTs) may be the gold standard in evaluating the effects of treatments. For the evidence presented in an RCT to be clinically relevant, the intervention evaluated must be deliverable to the specific patient population it is intended to be applied to, and the setting must have similarities to the setting where patients are actually located. Trials conducted in ideal settings with strictly limited criteria for study conduct may trade external validity for internal validity and so be less generalisable. Pragmatic trials, designed to evaluate treatments and care delivery in real world situations, may be more applicable to clinical practice, but may be unable to emulate high levels of internal validity due to practical constraints (Loudon, Treweek et al, 2015). Multiple factors can determine generalisability and applicability of RCTs including baseline patient population characteristics; geographical spread; the way a condition is diagnosed and classified; the presence of a range of long-term conditions in an ageing population and the co-prescribed items used to treat these; the availability and licensing of medicine regimens; health care costs; patient adherence and attitudes; staff availability, practice norms and attitudes.

Exploratory trials are designed to determine the presence or size of an effect under ideal circumstances. They therefore may not draw sufficiently on routine clinical practice to enable the recommendations arising from these studies to be integrated directly into a patient-focussed decision-making process. Random allocation to study intervention or control, allocation concealment and blinding strengthen internal but may compromise external validity (Gartlehner, Hansen et al, 2006).

This thesis and the research it presents therefore aims to provide pragmatic answers to guide the implementation of an HCV testing and treatment pathway in community pharmacies providing OST for PWIDs. It aims to do this by exploring the practicalities of delivering HCV care from a community pharmacy, taking into account the views and experiences of the patient cohort and staff , the interaction of the health system with the

people using it, within the broader policy context within the United Kingdom and internationally. It attempts to do this through the processes and procedures suggested by the Medical Research Council's Guidance on "Developing and Evaluating Complex Interventions", with development, feasibility and modelling stages, alongside implementation and evaluation activities (Craig, Dieppe et al 2008)

As a conceptual framework to understand the way that people, places and technology interact and to draw together the interactions of agency, power and culture, cognisance of Actor Network Theory (ANT) has been taken (Munro 2009). The consideration surrounding ANT: that it is the interactions of people with buildings and service configurations that determine behaviour and its consequences for health, has been most helpful in exploring practical ways to devise an effective care pathway within the complexities of a modern NHS.

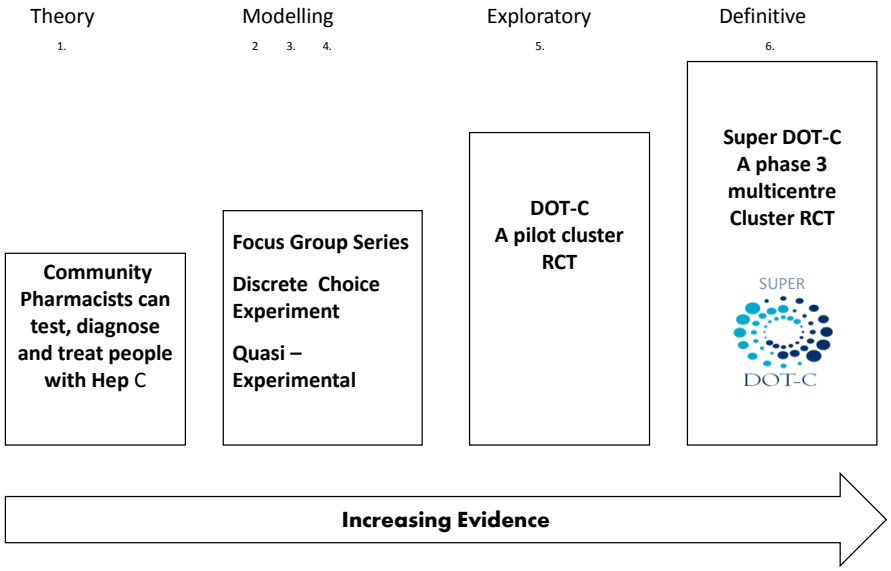
1.3 Thesis Structure and Content

Chapter 1: Introduction: the case for modelling, establishing and evaluating testing and treating Hepatitis C in Community Pharmacy, is intended to set out the context for Chapters 2-7. It has outlined the aims and objectives, structure and content as well as the underpinning constructs for its specific research focus. The next section of this chapter briefly presents the background that underpins the research that has been undertaken, so that the hepatology practice and chain of events leading up to the development of this thesis are highlighted.

Evidence presented in the thesis has been generated from a series of research projects undertaken to fulfil the objectives of a research fellowship provided by Gilead Sciences, and two research grants provided by Gilead Science, the Scottish Government and Bristol Myers Squibb. They were conducted and/or led during the period 2013-2018 by the author of this thesis. The results of this programme of research have been published as a series of papers and also conference abstracts. The author of this thesis is the principal author for all of these. The role of the principal author and all co-authors, is provided as part of the published manuscripts and in the supplementary information for chapters 2-7.

As described in Figure 1: Schematic outline of thesis structure and content, the purpose of the peer reviewed papers is to present generalisable evidence contributions of the programme of research to real-world policy development processes. A schematic for thesis structure and content is presented in Figure 1 below:

Figure 1: Schematic Outline for Thesis Structure and Content*



*adapted from MRC 2000

1.4 Background and Underpinning Practice for the Testing and Treatment of Hepatitis C

Hepatitis C (HCV) is a blood-borne viral infection (BBV) causing liver disease (WHO, 2016). It is most commonly transmitted through:

-Injecting drug use through the sharing of injection equipment;

-The reuse or inadequate sterilization of medical equipment, especially syringes and needles in healthcare settings; and

-The transfusion of unscreened blood and blood products.

HCV can also be transmitted sexually and can be passed vertically from an infected mother to her baby; however these modes of transmission are much less common. Hepatitis C is not spread through breast milk, food, water or by casual contact such as hugging, kissing and sharing food or drinks with an infected person.

The hepatitis C virus is an RNA virus that occurs as distinct geographical genotypes. There are eight confirmed HCV genotypes and 86 subtypes have been reported. 44% of infections with HCV worldwide and 60% of HCV infections in high-income and middle-income countries are of genotype 1. Around a third of genotype 1 infections occur in east Asia. Genotype 3 infections are more common in lower-middle-income countries (LMICs) than in high-income, upper-middle-income, and low-income countries, and they account for 25% of all HCV infections; around 75% of infections with HCV genotype 3

occur in south Asia. Genotype 4 infections constitute 15% of all HCV infections and they are most common in North Africa and the Middle East. Genotype 2 and 6 infections occur largely in east Asia. Genotypes 5, 7, and 8 comprise less than 1% of global HCV infections, with most cases originating in southern and central sub-Saharan Africa. HCV genotypes and subtypes respond differently to available therapies (Spearman, Dusheiko et al 2019)

Around 0.8% of the Scottish population are chronically infected with HCV (Scottish Intercollegiate Guidelines Network, 2013). The world-wide burden of HCV infection has been estimated as 71.1 million infections (62.5—79.4), with the largest group being genotype1 (Polaris Observatory HCV Collaborators 2017). The increased morbidity, mortality and economic impact of the infection are of concern to both industrialised and developing countries (Lavanchy, 2009).

The incubation period for hepatitis C is 2 weeks to 6 months. Following initial infection, approximately 80% of people do not exhibit any symptoms. Those who are acutely symptomatic may exhibit fever, fatigue, decreased appetite, nausea, vomiting, abdominal pain, dark urine, grey-coloured faeces, joint pain and jaundice (yellowing of skin and the whites of the eyes).

Due to the fact that acute HCV infection is often asymptomatic, few people are diagnosed during the acute infection phase. In those people who go on to develop chronic HCV infection, the infection is also often undiagnosed because the infection remains asymptomatic until decades after infection when symptoms develop secondary to serious liver damage.

HCV infection is diagnosed in 2 steps:

-Screening for anti-HCV antibodies with a serological test identifies people who have been infected with the virus.

-If the test is positive for anti-HCV antibodies, a nucleic acid test (polymerase chain reaction) for HCV ribonucleic acid (RNA) is needed to confirm chronic infection because about 30% of people infected with HCV spontaneously clear the infection by a strong immune response without the need for treatment.

After a person has been diagnosed with chronic HCV infection, they should have an assessment of the degree of liver damage (fibrosis and cirrhosis). This can be done by liver biopsy or through a variety of non-invasive tests including liver ultrasound (fibroscan) and assessment of liver biochemistry (Fib 4 / APRI). (Yen, Kuo et al, 2018)

People diagnosed as having an HCV infection should have the genotype of the HCV strain established by laboratory testing. There are 6 genotypes of the HCV. The genotypes have a specific geographical spread and may respond differently to the range of treatments that are available. Through transmission from different sources, it is possible for a person to be infected with more than 1 genotype. The degree of liver damage and virus genotype are used to individualise treatment decisions and guide the management of the disease.

Populations at increased risk of HCV infection include:

-people who inject drugs (PWIDs);

-people using intranasal drugs;

-recipients of infected blood products; recipients of invasive procedures in health-care facilities with inadequate standards of infection control;

-vertical transmission to children born to mothers infected with HCV ;

-Rarely, people with sexual partners who are HCV-infected;

-people with HIV co-infection;

-prisoners or people who have been previously incarcerated.

-people who have had tattoos or piercings from unsterilized equipment.

Hepatitis C infection may be cleared by the immune system of the person infected and some people with chronic infection may not develop liver damage or hepatocellular carcinoma. When treatment is necessary, the goal of hepatitis C treatment is cure. The cure rate depends on several factors including the strain of the virus and the type of treatment given. It is accepted that a cure is a Sustained Viral Response to antiviral therapy at twelve weeks after the course of antiviral treatment has been completed (SVR12) (Kozbial, Moser, and Al-Zoairy 2018)

The standard of care for hepatitis C is changing rapidly. Sofosbuvir, Daclatasvir and the Sofosbuvir/Ledipasvir combination are part of the preferred regimens in the WHO guidelines, and can achieve cure rates above 95%. These medicines are much more effective, safer and better-tolerated than the older therapies, which included pegylated interferon and ribavirin. Therapy with DAAs can cure most persons with HCV infection and treatment is shorter (usually 12 weeks). Newer DAAs currently being introduced can effect a cure across HCV genotypes and are less affected by the presence of liver disease than previous medicines.

A recent Public Health England report highlighted that less than 3% of those known to be infected with HCV are being treated and less than half of those infected are known

(Public Health England, 2018). The largest single infected group in the United Kingdom are those prescribed OST (Arain and Robaeys, 2014). Research suggests around 40% of people receiving OST in the United Kingdom have HCV (Aspinall, Doyle et al, 2015; Edlin, Kresina et al, 2005).

The paradigm shift resulting from the introduction of Direct-Acting Antiviral drugs (DAAs) has changed the narrative around HCV, with a realisation that HCV could be eliminated in people who inject drugs (Lima, Rozada et al, 2015). There is optimism that the use of DAAs offers a high chance of clearance of HCV infection from the population (Grebely and Dore, 2014). Treating all groups with HCV would yield substantial benefits (Van Nuys, Brookmeyer et al, 2014) but there are concerns that the infrastructure and treatment capacity to deliver the required health outcomes are not generally available or of insufficient scale (Leask and Dillon, 2016).

Treatment uptake for HCV amongst people who inject drugs is currently low (Wiessing, Ferri et al, 2014) and prospective patients may have a number of barriers to overcome in order to access care (Fernandez-Montero, Vispo et al, 2013). There are identified deficiencies in the extent of screening and diagnosis of at-risk populations, as well as improvements required in access to treatment initiation and clinical monitoring (Artenie, Jutras-Aswad et al, 2015): People who inject drugs may find it difficult to consistently attend medical clinics (Papatheodoridis, Tsochatzis et al, 2014). However, the delivery of HCV testing and treatment through community-based care pathways has been shown to be feasible (Wade, Doyle et al, 2016) and Dried Blood Spot Testing (DBST) has been demonstrated to increase the uptake of testing from high-risk populations (Coats and Dillon, 2015).

Creating the complex interventions necessary to eliminate HCV requires that well-designed cross-disciplinary programmes are put in place (Suther and Harries, 2015) using different strategies to increase screening, testing and diagnosis (Brouard, Le Strat et al, 2014). The potential of community pharmacy practices to make a greater contribution to the health of their local populations has been recognised for some time (Anderson, Blenkinsop and, Armstrong, 2009). Pharmacists have long had a major role in delivering OST to this group with a high prevalence of HCV (Anderson, 2007) and pharmacist involvement in delivering HCV treatment through multi-disciplinary clinics has been described for some time (Kolor 2005; Arora, Thornton et al 2011). People prescribed OST may see a pharmacist every day (Mathieson 1998). The relationships that are built through this daily interaction may have the potential to be utilised for wider therapeutic

purposes. With the availability of highly effective medicines with a low treatment burden to cure HCV and the daily interaction with a healthcare professional trained to deliver drug therapy, it is likely that current issues with access to and delivery of HCV treatment, could be addressed through use of a pharmacy-based pathway.

The Tayside region of Scotland has sequentially developed integrated HCV treatment services over the last two decades, moving from standard secondary care-based hospital outpatients, onto nurse-supported treatment services, then to a HCV managed care network (MCN) including a widespread dry blood spot testing programme in drug services and development in our outreach services across the region. This most recent development includes providing treatment within drug services and prisons (Tait, Wang et al 2017). The network aims for wide involvement in BBV testing and follow-up, with healthcare professionals such as drug workers, GPs, prison nurses and social workers taking the opportunity to discuss referral and treatment with patients.

Currently Pharmacists can signpost to testing and referral and some can offer HCV testing on site (Taheri 2010). Key barriers in the current NHS pathway are (i) low testing rates, (ii) poor linkage of those tested positively to treatment sites (a key factor being the limited number of treatment centres), (iii) staff perceptions of this group's ability to adhere to therapy attitudes and (iv) suboptimal adherence and persistence to the treatment. Cure of hepatitis C is defined by a sustained viral response (SVR) – no HCV RNA in the blood 12 weeks post treatment. The new all oral anti-HCV therapy (DAAs) are now available with cure rates greater than 95%, minimal side effects and no need for complex monitoring. These could be delivered in new environments via novel pathways. These regimens could be safely delivered by community pharmacists.

The World Health Organisation has provided an Advocacy Brief that sets out the actions required by Governments to achieve the Elimination Target of 2030 (WHO, 2016a). The brief notes that new medicines make the elimination of HCV possible. HCV is a leading cause of death through cirrhosis and hepatocellular carcinoma with mortality rising due to poor access to care. The WHO advocate that care pathways should be scaled up to meet assessed need and that innovation should be embraced to deliver wider access to care.

1.5 Factors Affecting the Habitus of Individuals Infected with the Hepatitis C Virus through Injecting Drug Use

The World Health Organisation has included the elimination of HCV as a public health concern by 2030 and governments are urged to invest in the health technologies available

to deliver this aim (WHO 2016b). However the numbers of people engaging with testing and treatment for HCV are low, despite the availability of effective cures with small treatment burdens and minimal monitoring requirements (EMCDDA 2016). The perception of a cure for HCV, as solely a clinical outcome, may in part explain the reticence of patients and payers to enthusiastically accept the advance in treatment provided by Direct-Acting Antiviral (DAA) medicines. The additional perspective of a cure, viewed from a social viewpoint may provide further compelling reasons to engage in HCV elimination (Rhodes, Harris et al, 2013)

The literature describes the many psychological, physical and social aspects of living with hepatitis C (Treolar and Rhodes 2009, Dowsett, Coward et al 2017). Experiences of stigma and discrimination are common for people who inject drugs, creating strong barriers to accessing HCV care and treatment (Fraser and Treolar 2007; Treolar, Rance and Backmund 2013). Physical and mental fatigue arising from HCV infection discourages a normal life and frames a person's social interactions (Groessl, Weingart et al 2008). Changes to employment status and social roles have implications for finances and morale, while relationships can be affected detrimentally, increasing feelings of isolation (Dunne & Quayle 2001). Many individuals reported negative experiences with the healthcare system; themes of feeling unsupported, not having adequate information, and not feeling involved in decisions are reported. (Harris, Van Essen and Litwin 2009). Participants may experience a reduced quality of life due to physical symptoms and all these factors contribute to people with HCV undertaking part-time work or not working (Hill, Pfeil et al, 2014).

Many authors have described the transformative experience of HCV cure and how people undergoing treatment are encouraged to take steps towards "a normal life" (Batchelder, Peyser et al, 2015). Interferon-based regimes require significant stoicism and resilience on the part of both patient and physician because of the burden of treatment. Undertaking a course of treatment with interferon-based regimes has a flavour of personal trial and rehabilitation (Clark and Gifford 2015) and many authors have discussed how the experiences have contributed to a change in personal perspective (Newman, Beckstead et al 2013; Rance, Treolar et al 2013; Rhodes, Harris and Martin 2013; Jones, Atkinson et al 2014, Maticic, Katelic et al 2014, Clark and Gifford 2015).

However, a narrative describing this transformation in the post-interferon era is difficult to identify in current literature, mainly because of the recent transition to the use of regimes containing solely DAA medicines. There is a potential paradox, in that the

DAA-based regimes provide a reliable cure, for a large majority of patients, with a relatively small treatment burden, but may not be a "personal trial" and may have a lesser impact on rehabilitation and recovery. Currently re-Infection rates may be only available marker of continuing drug-use post treatment (Grebely, Conway et al 2006) or failure of rehabilitation, but this indicator does not provide insights into the behaviours of recipients and of how treatment has changed their perspectives on their place in society. The success of attempts by the group cured of HCV, to progress down a recovery pathway and to resume activities thought of as being part of normal citizenship, are therefore unclear.

1.6 Funding of Studies Presented in This Thesis

The programme of research presented in this thesis has been undertaken with the benefit of funding gained through a series of fellowships and grants gained by the author. The details of these are presented below:

-Gilead Research Fellowships 2013-2015. Principal Investigator - Design and implementation of focus group series, discreet choice experiment, quasi-experimental study as preparation for pilot cluster RCT of directly observed therapy for treatment of HCV infection in community pharmacies. Andrew Radley and John Dillon. (£36k)

-Gilead Research Grant 2015-2016. Principal Investigator – Design and delivery of DOT-C: A cluster feasibility randomised controlled trial. Andrew Radley and John Dillon. (£247k).

-Scottish Government/ Gilead/ BMS 2015-2018. Principal Investigator - Super Dot-C. Phase 3 RCT of Community Pharmacy Pathway for Hepatitis C Treatment. Andrew Radley and John Dillon. (£16M)

Table 1: Schematic Outline of Thesis Structure

Chapter 1:

Introduction: the case for modelling, establishing and evaluating testing and treatment of hepatitis C in community pharmacy

Overview of content and rationale for inclusion**:**

This chapter sets out the aims and objectives of this research and the rationale for the approach taken in delivering the outcomes. The structure of the thesis is set out and an overview of the content described.

In defining the context for the research, the challenge of hepatitis C elimination is established, as defined by the World Health Organisation (WHO 2016a, WHO 2016b). Important factors influencing current health care practice for the treatment of people with HCV are briefly described, together with identified factors known to influence the uptake of the offer of treatment.

Research Objective

Can a pharmacist-led care pathway designed to test and treat HCV infection in people prescribed OST, increase the numbers of this population who access treatment and cure for hepatitis C?

Secondary Questions

What are the views and experiences of people who access pharmacy services to receive OST?

What are the important factors to be considered in the design of a pharmacist-led care pathway, from the perspective of the service-user population?

Can a pharmacy-based testing service for HCV infection encourage the target population of OST service users to take a test for blood borne viruses (BBVs)?

Is the delivery of a pharmacist-led pathway to deliver testing and treatment for HCV feasible?

How do service providers describe the provision of this service?

What causal mechanisms may be identified that impinge on the access to and delivery of effective care?

Chapter 2:

Developing and evaluating complex interventions

Overview of content and rationale for inclusion:

This chapter reviews the rationale for a systematic approach to the design, implementation and evaluation of complex interventions. Understanding of effective and

efficient design requires taking into account of the complexity of systems and their tendency to adjust to forces that impinge on them (Campbell M, Fitzpatrick R 2000). The Medical Research Council's Guidance on complex public health interventions acknowledges that an iterative approach to the design of an intervention is necessary, with planned stages of development to ensure that a subsequent experimental evaluation is robust and worthwhile (Craig P, Dieppe P et al 2006). Development of complex interventions should be informed by theory and their evaluation should take account of the context for delivery and the processes and human factors that may influence their implementation (Moore G, Audrey S et al 2008). It is included because it describes best practice in intervention design and sets the pattern for future work. The chapter outlines the methodological approach used, as well as the strengths and weaknesses of the research methods selected.

Chapter 3:

Delivering hepatitis C testing and treatment in community and primary care settings

Sources of Content:

Radley A, Robinson E, Aspinall EJ, Angus K, Tan L, Dillon JF. A systematic review and meta-analysis of community and primary-care-based hepatitis C testing and treatment services that employ direct acting antiviral drug treatments –BMC Health Services Research 2019 (19) 765. https://doi.org/10.1186/s12913-019-4635-7

Overview of content and rationale for inclusion:

The paper provides an overview of the evidence base describing the evaluations of care pathways that offer the newly introduced Direct Acting Antiviral (DAA) medicines into community and primary care environments. It reports the results of an updated systematic literature and meta-analysis of the first studies to be published after the marketing of these medicines in 2013. The World Health Organisation Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection, promote simplified service delivery models; integration with other services; decentralised services supported by task-sharing and community engagement to address stigma and increase reach. task-shifting to non-specialist clinicians. It is included because it demonstrates the current status of implementation of the changes required to achieve the WHO goals, from published evidence

It is included because it demonstrates that initial steps have been taken to implement these guidelines, but that strong evidence based on experimental study designs is currently lacking

A critical reflective section is included with a critique of methods and of analysis, building on the discussion in Chapter 2.

Chapter 4:

Development and modelling of an intervention in community pharmacy

Sources of content:

Radley AS, Melville K, Easton P, Williams B, Dillon JF. "Standing Outside the Junkie Door" – Services users experiences of using community pharmacies to access treatment for opioid dependency. J. Public Health 2016 doi:10.1093/pubmed/fdw138

Radley A, van de Pol M, Dillon JF. Designing a hepatitis C testing service in primary care: a discrete choice experiment. International Journal Of Drug Policy 2019; 65:1-7. https://doi.org/10.1016/j.drugpo.2018.12.008

Radley AS, Melville K, Tait J, Stephens B, Evans JEE, Dillon JF. A quasi-experimental evaluation of dried blood spot testing through community pharmacies in the Tayside region of Scotland. Frontline Gastroenterology 2017 doi: 10.1136/*flgastro-2016-100776*

Overview of content and rationale for inclusion:

These papers outline pilot and feasibility work undertaken to develop and describe the pharmacist-led intervention, as part of the process of acquiring increasing evidence to inform the design of a definitive experimental study.

The paper describing a focus group series illustrates the lived experience of people prescribed opioid substitution therapy and identifies a variety of themes that form a basis for a grounded approach to co-design of the intervention.

The paper describing a discrete choice experiment utilises themes identified from the focus group series plus several structural themes and evaluates the preferences of a cohort of people prescribed opioid substitution therapy for the design of a pharmacist-led intervention. The method provides an estimate of the additional uptake predicted by the preferred model.

The paper describing a quasi-experimental approach to blood-borne virus testing in pharmacies demonstrates the implementation of the first part of the intervention and explores initial participant and provider views about delivery.

These papers are included here to record how the pilot and feasibility work have shaped and informed the subsequent development of the SuperDOT-C intervention.

A critical reflective section is included with a critique of methods and of analysis, building on the discussion in Chapter 2

Chapter 5:

Feasibility assessment and evaluation of a care pathway for testing and treatment of hepatitis C infection in community pharmacies.

Sources of content:

Radley A, Tait J, Dillon JF. DOT-C: A Cluster Randomised Feasibility Trial Evaluating Directly Observed Anti-HCV Therapy in a population receiving opioid substitute therapy from community pharmacy. International Journal of Drug Policy 2017; 47: 126-136. doi: 10.1016/j.drugpo.2017.05.042.

Radley A, de Bruin M, Inglis S, Donnan PT, Dillon JF. Clinical effectiveness of pharmacy-led versus conventionally delivered antiviral treatment for hepatitis C in patients receiving opioid substitution therapy: a study protocol for a pragmatic cluster randomised trial. BMJ Open 2018; 8:e021443. doi: 10.1136/bmjopen-2017-021443

Radley A, de Bruin M, Inglis S, Donnan PT, Hapca A, Barclay ST, Fraser A, Dillon JF. Clinical effectiveness of pharmacy-led versus conventionally delivered antiviral treatment for hepatitis C in patients receiving opioid substitution therapy: a pragmatic cluster randomised trial (Submitted Lancet Gastroenterology and Hepatology 2020).

Overview of content and rationale for inclusion:

These papers outline the feasibility assessment and evaluation of the designed care pathway using a cluster randomised controlled trial methodology to evaluate causation. Causal inferences indentified through the course of the programme of research are defined and supported with evidence gained through the qualitative research elements that have been undertaken.

The paper describing the feasibility trial evaluates the implementation of the care pathway as a whole process. The process evaluation describes the views and perceptions recorded by participants and staff members through their experiences receiving and providing care.

The study protocol sets out the intentions and experimental procedures undertaken to deliver a multi-centre cluster randomised controlled trial, documenting the plans for analysis and governance provisions for safe and ethical research.

The outcomes of the definitive cluster randomised controlled trial, as an endpoint of the programme of research are set out in the penultimate paper, together with details of the process analysis and an economic analysis

A critical reflective section is included with a critique of methods and of analysis, building on the discussion in Chapter 2

Chapter 6

Mapping of Causal Inferences Identified During the Development and Evaluation of a Complex Public Health Intervention

Sources of content

Radley A, Inglis Sk, Dillon JF. Using a systems-thinking approach to elucidate programme theory underpinning the effectiveness of the SuperDOt-C Intervention: a pharmacy-led test and treat pathway for PWIDs with hepatitis c infection prescribed opioid substitution therapy.

Overview of content and rationale for inclusion

This paper brings together the insights and learning developed from the evaluative and experimental work carried out through this programme of research. The elements identified from the published studies are conceptualised visually as a causal loop diagram. A critical reflective section is included with a critique of methods and of analysis, building on the discussion in Chapter 2

Chapter7

Discussion and Conclusion

Overview of content

This chapter provides a summary and reflection on the programme of study with a discussion of strengths and weaknesses. A summary of the unique contribution to knowledge in this area is set out. A summary of knowledge and evidence contributions of the thesis to policy development and scholarship is given as well as a narrative about the development, processes and decisions made in delivering this programme of study. An account of future plans is provided.

Chapter 8

Bibliography

A full list of sources used in this thesis is provided

Chapter 9

Appendices

Copies of published papers are provided

CHAPTER 2

DEVELOPING AND EVALUATING A COMPLEX HEALTH CARE INTERVENTION

Complexity in a system is determined by such factors as the number of components and the intricacy of the interfaces between them, the number and intricacy of conditional branches, the degree of nesting, and the types of data structures. A complex system is one in which there are multiple interactions between many different components. Complex systems are observed to have a number of consistent properties including non-linearity, where the interaction of two components are not the sum or product of its parts; where feedback from interaction of its components changes its state; where spontaneous order arises from the random aggregation of a large number of uncoordinated interactions; where the complex system is stable and robust in the presence of forces exerted on it; and its has many levels of hierarchy and a tendency to increase in complexity.(Ladyman and Wiesner 2013) Within complex systems, the term "feedback" describes the situation in which a change reinforces or balances further change. Also, the term "adaptation" refers to adjustments in behaviour in response to interventions. This includes the operations, structures and relations that exist in each setting.

A complex systems model of public health conceptualises poor health and health inequalities as the outcomes of a multitude of interdependent elements within a connected whole. These elements affect each other in sometimes subtle ways, with changes that have consequences for the whole system (Petticrew 2011).

Therefore for areas of interest to public health, complexity is a property of the system or environment in which an intervention operates, rather than for the intervention itself. Such a system is adaptive to changes in its local environment, is composed of other complex systems, and behaves in a non-linear fashion. Interventions in complex systems may be simple or complicated, but there will be an interaction between the intervention and the context in which it is implemented. The properties of a complex system cannot be entirely predicted from the elements within it and are more than a sum of its parts. Complex interventions are widely used in health services, in public health practice and in areas of social policy. Complex interventions are built up from a number of components which may act both independently and interdependently. Randomised trials of complex interventions have a number of interacting components within the experimental and

comparator interventions; they require performance of a number of behaviours of differing complexity; different groups or organisational levels are targeted; there are a number of outcomes; the intervention may require to be flexed or tailored to individual contexts.

Acceptance of a complex system approach necessitates use of a broad spectrum of methods to design, implement and evaluate interventions that aim to change these systems and improve public health. The properties of a complex system mean that it is stable and robust when external forces are applied to it, however, it can adapt and change through feedback provided through the interaction of its components. Instead of evaluating whether an intervention works to fix a problem, researchers should aim to identify how it contributes to reshaping a system in a favourable way. Evaluations should take account of the complexity of systems (Rutter, Savona et al 2017). The context for implementation has implications for the design and evaluation of an intervention (Shiell, Hawe and Gold 2008). Consideration of complexity changes focus away from simple, linear causal models to concern about the ways in which processes and outcomes at all points within a system drive change

2.1 Developing Complex Interventions

The Medical Research Council (MRC) published its first Framework for design and evaluation of complex interventions to improve health in 2000 (MRC 2000; Campbell, Fitzpatrick et al, 2000). These guidelines recognised that a complex system approach required the use of a broad spectrum of methods to design, implement and evaluate interventions. They identified that evaluation of complex interventions is difficult because of problems of developing, identifying, documenting, and reproducing the intervention; a phased approach to the development and evaluation of complex interventions is required to help researchers define clearly where they are in the research process and also that evaluation of complex interventions requires use of qualitative and quantitative evidence

It is established that complex interventions are those that consist of a number of components that may act both independently and interdependently. In taking account of this conceptualisation, the Medical Research Council emphasizes the importance of early phases of developing the intervention, measures and trial design. Developing phase one (review of theory) and phase 2 (modelling the intervention) (Craig, Dieppe, et al, 2008) are key steps.

2.1.1 Causal modelling

In understanding the operation of an intervention, causal modelling can be used to guide the design of a programme to support behaviour change for trial evaluation. Causal assumptions may be drawn from social science theory, but should also be informed by other factors such as experience and common sense (Suzuki and Vanderweele 2018). Explicitly stating casual assumptions about how the intervention will work can allow external scrutiny of its plausibility and help evaluators decide which aspects of the intervention or its context to prioritise for investigation. The relationships between implementation, mechanism and context may be interdependent as a complex system (Rutter, Savona, et al, 2017).

Causal models should span behavioural determinants, health outcomes and their correlates: behaviour; physiological and biochemical variables; and health outcomes (Bonell, Melendez-et al 2018). Evidence about causal mechanisms can be described in a causal loop diagram that sets out the different influences that affect the performance of an intervention. (Yourkavitch, Hassmiller, et al 2018; Renmans, Holvoet and Criel 2017) Mechanisms are particularly important in understanding the explanation of causal processes. Causation is a multifactorial phenomenon. It is the combination of numerous conditions that give rise to health and social care outcomes (Suzuki and Vanderweele 2018).

A generic causal model can be derived from an epidemiological perspective to describe a causal pathway from behaviour to outcome (Hardeman, Sutton et al, 2005). Examples can be drawn from the treatment of hepatitis C (Table 2).

Table 2: Generic causal model *

Level		Methods
1.	Behavioural determinants	Defining the health outcome, its importance and predictors e.g. injecting drug use; receipt of opioid substitution therapy (OST)
2.	Behaviour	Defining the target group e.g. people who use drugs; people who receive OST
3.	Physiological and biochemical variables	Identification of the target behaviour and the likely impact of achievable behaviour change on physiological and biochemical variables e.g. attendance to receive OST; recovery from addiction;

		adherence to anti-viral drug treatment (Direct Acting Antivirals, DAA)
4.	Health Outcome	Development and validation of precise objective measures of the target behaviour e.g. Achievement of a sustained viral response to DAAs

* Adapted from Hardeman, Sutton et al, 2005

Causal models extend the MRC Framework in several ways (Hardeman, Sutton, et al, 2005):

-They guide the choice of intervention points and measures

-They assist in the choice of behaviour change techniques

-They inform the assessment of fidelity to theories

-They enable statistical modelling of relationships between measured behaviours and health outcomes.

The methods that can be used in the development of a causal model are show in Table 3

Table 3: Methods used in the development of the causal model

General Methods		Specific methods
1.	Defining the health outcome and importance	Review of the epidemiological evidence about the importance of the health outcome
2.	Specifying the physiological and biochemical variables	Review the evidence about the physiological and biochemical risk factors
3.	Defining the target population	Review of epidemiological evidence of determinants of the disease. Development of a feasible and acceptable strategy to identify individuals in the target group from the population. Engage with stakeholders and partners to co-produce approach
4.	Developing objective measures of the target behaviour	Identification of objective measures of desired outcome. Review of known behavioural determinants. Consultation with target group about the acceptability of the intervention.
5.	Specifying theory based behavioural	Development of criteria for selection of theory. Assessment of systematic reviews

	determinants	
6.	Specifying the intervention points	Development of matrices for objectives, intervention methods and strategies
7.	Specifying the behaviour change techniques	Use of published evidence and expert opinion
8.	Developing measures to assess change in behavioural determinants	Review of salient beliefs form the target group for engagement with the intervention. Development of a process evaluation approach to assess presumed intervention components

* Adapted from Hardeman, Sutton et al, 2005

2.2 Phased development of a complex intervention

Different approaches can be used for intervention development and evaluation and include mapping techniques of various kinds including logic models (Conrad, Randolph, et al, 1999) and different matrices for objectives, intervention methods and strategies. Operationalisation may occur within a pilot randomised trial or feasibility study of the intervention.

The phased development of a complex intervention may be iterative or cyclical (Levin, Xepapadeas et al, 2013). Existing evidence should identify what is already known about similar interventions and the use of similar methods in the area of interest. High quality systematic reviews can be utilised to summarise evidence or undertaken to provide an assessment of evidence.

As part of the process for developing a complex intervention, the rationale for developing a complex intervention, the change that is expected to be delivered and the route by which that change is to be achieved should be explored using existing evidence and theory. New primary research can be used to inform gaps in existing knowledge.

A number of limitations have been identified in the original MRC guidance and led to a revised document being published in 2008 (Craig, Dieppe, et al, 2008). The key change in focus lies around the recommendations: for greater attention to be paid to early phase piloting and development activities; a less linear model of evaluation and integration of process and outcome evaluations. There is an acknowledgement that complex interventions need to be adapted to local contexts rather than be completely standardised

and also that the theory of complex adaptive systems could provide some insight (Levin, Xepapadeas et al, 2013).

Randomisation is a powerful tool that can facilitate estimation of average causal effects even in the face of complexity and uncertainty. Randomised controlled trials (RCTs) allocate individuals or clusters of individuals to different groups, exposing them to new, existing or no interventions. Randomisation prevents systematic bias in allocation and aims to minimise chance imbalances (Bonell, Melendez-Torres and Quilley 2018).

However RCTs alone may be insufficient to understand how the efficacy of an intervention in a trial situation can be translated into an effective intervention in a real world context. Effective deployment of trial evidence also requires that there is an understanding mechanisms of action and the performance of the intervention in different contexts.

A series of studies may be required to progressively gain an understanding of the way an intervention is designed and to optimise the way it performs. An economic analysis that indicates that an intervention is unlikely to be cost-effective would provide evidence that it should not be developed further in the same way.

2.3 Process evaluation

Process evaluations which explore the way in which a study is implemented will provide insights and possible explanations into the way an intervention performs and why factors involving acceptability, compliance, delivery, recruitment and retention have occurred. A process evaluation undertaken within a trial can be used to assess the fidelity and quality of implementation, inform the understanding of causal mechanisms and the contextual factors associated with site-by-site variation in outcome (Craig, Dieppe et al 2008).

RCTs may be regarded as the gold standard for establishing the effectiveness of interventions, where randomisation is possible. However effect sizes do not provide policy makers with information on how an intervention might perform in their specific context and whether trial outcomes will be reproduced.

The updated Medical Research Council Guidance recognises the value of process evaluation within trials to assess the fidelity and quality of implementation, clarify causal mechanisms and identify contextual factors associated with variation in outcomes (Craig, Dieppe et al 2008).

Process evaluations can usefully investigate how the intervention was delivered and provide policy makers with information about how the outcomes may be replicated in

their particular context. Context is anything external to the intervention that may act as a barrier or facilitator to its implementation and effects. Understanding context is critical in interpreting the findings of a specific evaluation and generalising beyond it. Issues to be considered include training and support, communication and management structures and the interaction with implementer's attitudes and circumstances.

During a process evaluation, evaluators need to be close enough to the intervention to record problems, but sufficiently independent to report these to intervention stakeholders. Initial analysis of the process data should be conducted before the outcomes analysis to avoid biased interpretation of process data.

Process evaluations also commonly investigate the reach of interventions, that is, whether the intended audience comes into contact with the intervention and how. Process evaluations may test hypothesised causal pathways using quantitative and qualitative data to understand complex pathways and identify unexpected mechanisms (Moore, Audrey et al 2015)

The MRC Framework has a strong focus on clinical trials and conceptualises five phases representing a continuum of increasing evidence when developing an intervention. The MRC Framework recommends a feasibility and piloting phase to test the proposed intervention. During this phase, a process evaluation has a role in understanding the feasibility of the intervention and optimising its design and evaluation. However the next stage shifts the focus of a process evaluation onto providing greater confidence in conclusions about effectiveness by assessing the quantity and quality of what was delivered and assessing the generalisability of its effectiveness by understanding the role of context. A process evaluation will be needed to accompany a full trial, since new problems are likely to emerge.

Process models are used to describe or guide the translation of research into practice. Early process models tend to depict implementation as a rational liner process. A more sophisticated approach to process modelling identifies that facilitation is required, with emphasis placed on the context in which research is implemented and used.

It is useful to report assumptions about how the intervention works, ideally in a logic model and how these informed the selection of research questions and methods (Moore, Audrey et al 2015).

2.4 Phases of intervention development (MRC Guidance)

The MRC Guidance is presented as a number of phases in which researchers gain a progressively greater understanding of how the proposed intervention will perform:

Preclinical / theoretical phase – The first step is to identify the evidence that the intervention might have the intended effect. Review of the theoretical basis for an intervention and development of the hypothesis with more detailed specification of the potential active ingredients. Previous studies may provide empirical evidence.

From an evaluation perspective, a theory is a set of analytical principles or statements designed to structure an observation, understanding and explanation of the world. A theory usually describes some kind of predictive capacity (Nilson 2015). Theories can inform a hypothesis about causal processes and therefore allow researchers to explicitly test whether they hold or not. Theories can also offer insights into contextual conditions in which the intervention is likely to work. Overarching unified theories might explain all observed uniformities of social behaviour, social organisation and change. Theories that could be described in this way might include functionalism, symbolic interactionalism and social exchange theory. Theories regarding collective and aggregate levels are relevant in implementation. Examples may include social network theory and social capital theory (Holman and Borgstom 2016).

Middle range theories include Realist Evaluation (Pawson and Tilley 1991), which is framed as a theoretical approach to practical realism: what works for whom and in what context. Realist research demonstrates the interplay between policy, programme or intervention, context, actors, causal mechanisms and outcomes (Van Belle, van de Pas and Machal. 2017)

A realist approach seeks to identify what works, for whom and in what circumstances as a causal explanation of the relationship between context, mechanism and outcomes, rather than to seek causal relationships between intervention and effect (Harvey, Kitson et al 2015; Carlile 2002)

Critical realist sociologists view mechanisms as causal processes that can trigger events; contingently dependent on interactions with other mechanisms operating in a context. Interventions can be theorised to operate in terms of how the mechanisms that an intervention aims to trigger will interact with context to generate outcomes. Realist evaluators suggest that evaluations should test hypotheses about *context-mechanism-outcome* configurations to assess what works for whom and under what circumstances.

Economists theorise that behaviour is enabled or constrained by money. Sociologists would broaden this to a theorising agency in which formal and informal rules and rituals shape social interactions. Evaluators should be aware of the contingency of mechanisms, dependent not only on context but also the agency of those providing and receiving interventions. Mechanisms are concepts that form an integral part of causal explanations (Bonell, Melendez-Torres and Quilley 2018)

Poor theoretical underpinning makes it difficult to understand and explain how and why implementation succeeds or fails, thus restraining opportunities to predict the likelihood of implementation success and develop better strategies to achieve more successful implementation. Implementation is part of a diffusion-dissemination-implementation continuum, where diffusion is passive, untargeted and unplanned (Nilson 2015).

Phase 1 – defining components of the intervention. Modelling and simulation techniques can improve understanding of the components of an intervention and how they may interact. Qualitative approaches such as focus groups, surveys and interviews may help define components. Qualitative research may also be useful in defining how the intervention may work and what the associated barriers and facilitators may be.

Phase 2 – Defining trial and intervention design – Information about acceptability of the intervention to potential providers and participants and feasibility of the components of the intervention being delivered. This is particularly important where health services may deliver a number of care pathways and patient treatments. Feasibility studies are used to develop optimum intervention and evaluation design. Research sites should develop an understanding of the intervention and how it is delivered. Exploratory trials can also be used to determine the consistency with which the intervention is enacted. The learning from these activities is used to ensure that the intervention is provided effectively (Campbell, Fitzpatrick, Haines, Kinmonth, Sandercock, Spiegelhalter, Tyrer 2000.

It is important to demonstrate the effectiveness of the intervention and to understand the implementation process, the causal processes that underlie the intervention and the deeper societal change they envisage.

A range of models and frameworks have been proposed in order to support effective intervention. A model is a deliberate simplification of a phenomenon that describes rather than explains behaviours. A Framework usually denotes a structure, overview, outline, system or plan consisting of descriptive variables that are presumed to account for a phenomenon (Nilson 2015)

Determinant frameworks describe the general types of determinants that are hypothesised to influence implementation outcomes. For example, the Theoretical Domains Framework was constructed on the basis of a synthesis ofm128 constructs related to behaviour change. The constructs are sorted into 14 theoretical domains. The Theoretical Domains Framework does not specify the causal mechanisms of an intervention. Determinant Frameworks indicate that multiple levels of influence across relationships, systems and organisations.(Michie, van Stralen, West et al 2016)

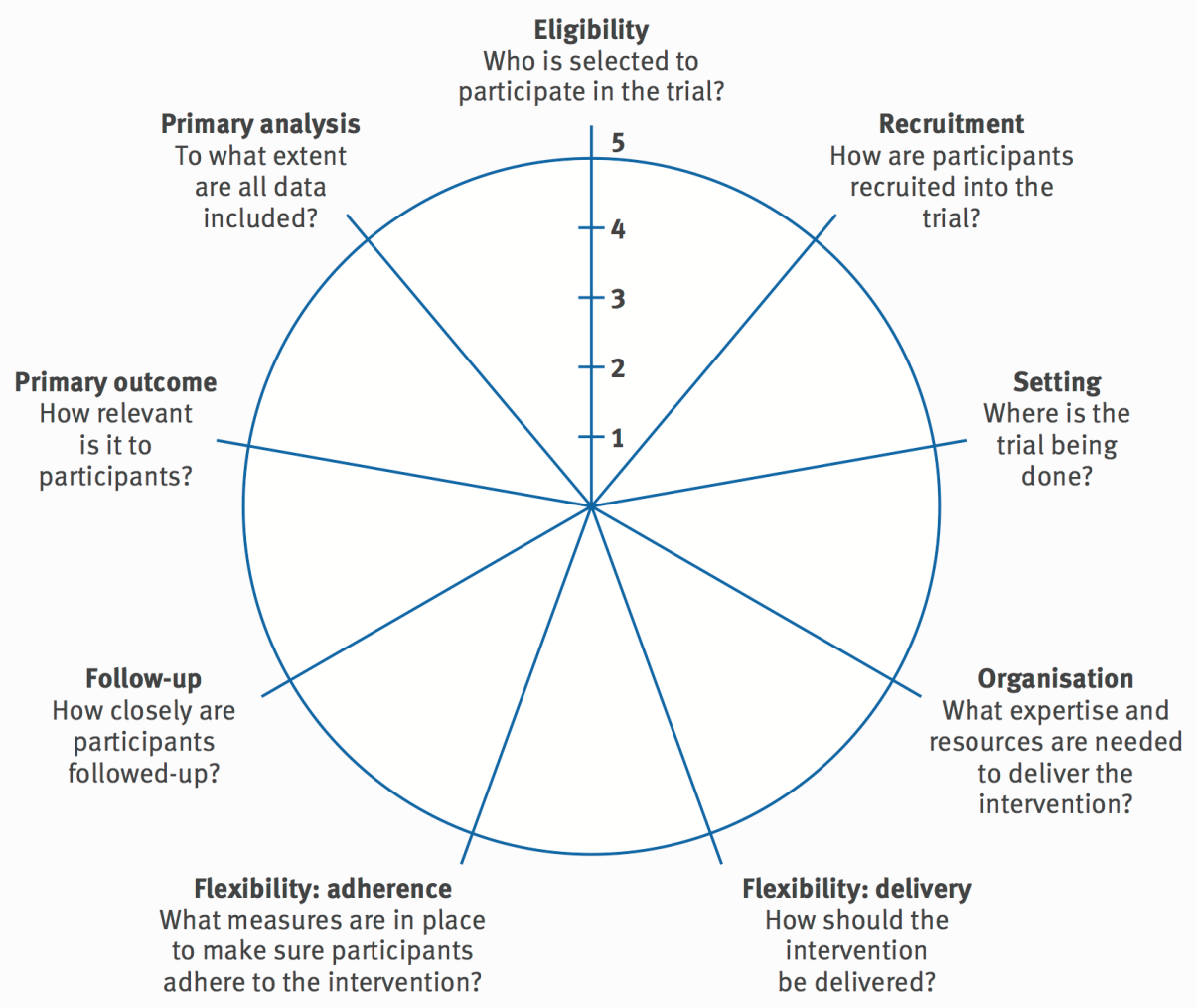
Table 4: Framework for the development and evaluation of complex interventions*

Phases		Methods
1.	Pre-clinical/theoretical	Review relevant theory and evidence to ensure best choice of intervention and predict major confounders and strategic design issues
2.	Modelling	Identify intervention components and inter-relationships and link to potential outcome measures
3a. 3b.	Operationalisation Piloting exploratory trials	Describe components of a replicable intervention Describe a feasible trial protocol for comparing the intervention to an appropriate alternative
4.	Definitive RCT	Compare a fully-defined theory-based intervention to an appropriate alternative using a protocol that is reproducible, adequately controlled and statistically powered
5.	Long-term implementation	Determine whether the intervention and results can be reliably replicated in uncontrolled settings over the long-term.

*adapted from Campbell, Fitzpatrick et al 2000).

The PRECIS-2 tool is also used to provide guidance to evaluators when designing trials, to help ensure that they are translatable into practice. (Loudon, Treweek et al, 2015) The PRECIS-2 model is intended to support researchers make design decisions consistent with the intended purpose of their trial. It uses a wheel format, with nine domains—eligibility criteria, recruitment, setting, organisation, flexibility (delivery), flexibility (adherence), follow-up, primary outcome, and primary analysis—scored from 1 (very explanatory) to 5 (very pragmatic) to facilitate domain discussion and consensus (see figure). The tool therefore takes researchers through the process of explicitly matching of design decisions to how the trial results are intended to be used (www.precis-2.org)

Figure 2: the PRECIS Wheel



2.5 Evaluating success in implementation

Evaluation frameworks provide a structure for evaluating implementation e.g. RE-AIM. They specify implementation aspects that should be evaluated as part of intervention studies (Nilson 2015).

The RE-AIM evaluation model focuses on the public health impact of interventions and its parameters are considered in MRC phases three to five. The Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM) framework was designed to improve reporting on key issues involving implementation and external validity.

Reach refers to the participation rate within the target population and the characteristics of participants as opposed to non-participants. Factors determining reach may include cost, referrals, scheduling, transportation and inconvenience. Efficacy is the impact of an intervention on specified outcome criteria. Adoption is a systems level measure concerning the number and representativeness of organisations taking up the intervention.

Factors determining adoption include cost, level of resource and expertise required and similarity of services to current provision. Implementation refers to intervention integrity: the quality and consistency of delivery. Maintenance reflects how well behaviour change efforts are sustained in the long-term.

Programme planners should make decisions regarding implementing and funding health services based on multiple dimensions, rather than only considering efficacy in randomised controlled trials (Glasgow, McKay et al 2001).

A range of other models are also advocated: Precede-Proceed specifies a needs assessment that maps across to MRC Framework phase 1. Logic models link inputs and activities to programme outputs and outcomes, whilst communicating the theory behind the programme; these are activities in the MRC Framework phases one to four (Hardeman, Sutton et al 2005).

Evidence translation into practice is rarely straightforward and linear: the contestable nature of evidence; the multiple influences on decision making; the effect of contextual variables at a micro, meso and macro level. Translation strategies therefore often favour multi-faceted approaches.

The PARIHS framework – Promoting Action on Research Implementation in Health Services – proposes that successful translation occurs when a combination of factors come into play (Rycroft-Malone, Seers et al 2013). These include how robust the research evidence is and how it reflects clinical, patient and local evidence, the receptivity to new ideas, the prevailing culture, leadership, orientation to evaluation and learning and then how the adoption of new evidence is facilitated and by whom. Where the environment for evidence adoption is challenging, then sophisticated skills in consensus building, negotiation and conflict management may be required. Translation is fundamentally about enabling others to act.

The characteristics of knowledge that drive innovation within a function actually hinder problem solving and knowledge creation across function (Carlile 2002). Syntactic boundaries are where differences in language and terminology create boundaries and are addressed when a common syntax is found. Semantic boundaries occur when there are differences in interpretation. Successful address may require attempts to identify a common meaning. Pragmatic boundaries occur when there is a high degree of novelty involved. Take-up of new knowledge is seen to involve acquisition of new costs by some stakeholders. Teams may have to adapt their existing domain-specific knowledge, leading to processes of contestation and negotiation, involving issues such as power,

vested interests, roles and relationships: new knowledge challenges assumptions and understanding.

Many interventions found to be effective in prevention and disease management research fail to be widely adopted or translated into meaningful outcomes. Barriers to wide-scale implementation arise at multiple levels: citizens and patients; the practitioner and staff; organisational and community; and policy levels(Treweek and Zwarenstein 2009). Normalisation Process Theory (NPT) has been used to explain the success or failure of implementation projects, and is most often used retrospectively as an organising framework for analysis and reporting of findings (De Brun, O'Reilly et al 2016) can be used as a learning device to critically interrogate experience and data. The theory uses four overarching constructs: coherence (sense-making), cognitive participation (engagement), collective action (enactment) and reflexive monitoring (appraisal). Best practice use of Normalisation Process Theory in intervention design is to engage with multiple stakeholders and to co-produce implementation processes from a range of perspectives. The use of NPT has been linked to participatory learning methods in this context, to facilitate the commitment of the range of contributors to the research.

2.6 Actor Network Theory

Actor–network theory (ANT) is a theoretical and methodological approach to social theory which asserts that everything in the social and natural worlds exists in constantly shifting networks of relationships (Holman, Borgstom et al 2016). It takes a position that nothing exists outside those relationships. All the factors involved in a social situation (human and non-human) are on the same level (they have symmetry), and there are no external social forces beyond what and how the network participants interact at present. Thus, objects, ideas, processes, and any other relevant factors are seen as just as important in creating social situations as humans. ANT holds that social forces do not exist in themselves, and therefore cannot be used to explain social phenomena (Latour 2005).

ANT envisages that social, psychological and physiological process can shape a situation. But also elements as diverse as the workplace, a life event, or political change can shape the form and content of relationships (Torronen, Tigersted et al, 2018). These contributing elements, both human and non-human, are called actors. In ANT, the assemblage of actors form a network that can direct, influence and transform action. ANT examines relational linkages as situational network-related dependencies between

actors. In real life, events are moved forward by heterogeneous and unpredictable interactions between human and non-human assemblages. Action is therefore understood as "a conglomerate of many surprising sets of agencies that have to be slowly disentangled"(Latour 2005). The actors that actively combine are termed mediators. By connecting two or more mediators, ANT brings forward a modification or translation to a system. Entities achieve their form and meaning only in relation to other entities (Law 1999). ANT explores the multiple networks between human and non-human actors; how they are established, evolve, interrelate and move. The goal of ANT is therefore to expose the actions, relations and processes that enable subjectivities, objects, effects, technological innovations and states of affairs to emerge and stabilise in networks. ANT requires that every observable phenomenon exists thanks to its relations: actors only have an ability to act from what is around them (Duff 2013).

ANT has been used to conceptualise the use of alcohol from the standpoint of a focus on relationships. Existing perspectives often reduce alcohol dependence to a series of influencing factors including genes; physical dependence; a psychological disorder; will power family or social problems. An analysis from an ANT perspective might mobilise human relationships as well as actors from community and government levels e.g. education; transportation; workplace; urban planning; welfare. Entities such as knowledge; resources and communications technology might also be considered (Torronen, Tigersted et al 2018). ANT therefore provides scope for material and biological factors, as well as the human ingredients, to be considered in gaining an understanding of alcohol addiction. The broader contexts of drug use have also been considered using ANT which can be used to describe how subjects, activities, agencies, networks and spaces are produced in and through the activity of drug consumption (Duff 2013). An ANT analysis examining the adherence of people with AIDS to their treatment concluded that taking the medicine was the least of the problems facing this patient group (Rossi and Pereira 2014)

The way that health services form relational linkages with human and non-human actors can also be considered from an ANT perspective. Services comprise of socio-technical (human and technological) factors which exchange various resources and competencies. Service networks mediate transfer resources and competencies, and cause translations in networks with positive or negative outcomes. Service networks become increasingly complex when technology is implemented to execute specific processes to deliver a service (Carroll, Richardson and Whelan 2013). ANT has been applied to care pathways

for asthmatic patients, considering the use of a metered dose inhaler (Prout 1996). This analysis describes how the networks of actors (pharmaceutical scientists, doctors, pharmacists, nurses, manufacturing plant, distribution lorries, treatment guidelines) leading to the provision of the inhaler, are effaced in order that the flow of life can continue (punctualisation). The teaching of the patient to effectively us the inhaler is described as "configuring the user". The successful endpoint of the relational interactions with the indefinite number of networks and the patient is successful delivery of an asthma medication.

ANT is a useful tool for appraising complexity and analysing the production of change in health care, since it deals with systems made of human and non-human entities and proposes a relational view of action; it provides an understanding of the intervention-context interaction; and understanding how interventions produce their effects (Bilodeau and Potvin 2018). ANT promotes the conceptualisation of context in relation to networks of actors and their actions. . It is not the actors themselves that are the focal point, but the connections between them, through which they act. Understanding the processes involved in producing effects assists the understanding of complexity.

ANT has been used as a quality improvement tool in healthcare systems, where an understanding of the way that human and non-human actors interact enables a more comprehensive picture of the requirements for successful implementation to be built (Booth, Andrusyszyn et al 2016). One of the main benefits is how the theory helps understanding of social effects are generated through the interactions of different actors in a network: that the interactions of human and non-human entities produces an outcome that would not be explained through consideration of either actor separately.

In the context of complex public health interventions, ANT concentrates on the processes responsible for producing the effects of interventions, based on the premise that the observable changes are the end results of the interactions of human and non-human actors. Bilodeau and Potvin 2018) Since of human and non-human actors are capable of agency, depending on how they are associated within a network, ANT allows the scientific evidence, expert opinion, financial resources and regulation to be considered a s shaping a public health intervention. The premise of symmetry in ANT means that the interactions of human and non-human actors are intertwined.

ANT refers to the linkage that connects disparate entities (e.g. humans, objects, ideas, interest, values) as translations. Translation is the process by which networks are created, expand and act (Latour 2005). The translation process is said to consist of four non-

linear processes: problematization (identifying the relevant entities to a situation); Interessement (rallying the actors); Enrolment (successful engagement of actors); Mobilisation (achieving a critical mass for action) (Craine, Parry et al 2009).
ANT provides the understanding that an effective public health intervention requires transformative processes in complex systems. A range of actors are required to come together to co-produce the knowledge and actions to deliver change. The human and non-human actors must be considered in planning and understanding the mechanism for the intervention and mediation of the change is delivered by the interaction of these elements in the complex system (Bilodeau and Potvin 2018). Studies that evaluate complex interventions should consider ANT as part of the underpinning theory that guides the intervention design and accompanying process evaluation.

2.7 Methods Employed

The publications in this thesis have used a series of qualitative, quantitative and mixed methods approaches to addressing the defined research questions. Qualitative and quantitative research approaches have differing fundamental assumptions about the way we know things and about what things are. Quantitative research requires a systematic way to approach the classification of size and number and draws on a positivist view of knowledge. Positivism is centred around a view that only things that are measurable actually exist and that an objective view of the world can be constructed. Qualitative research uses a range of approaches to gain insights into the meanings, concepts definitions, characteristics, metaphors, symbols, and description of things (Pope and Mays 2006). Triangulation of data provided by using different qualitative and quantitative methods supports the development of different insights and knowledge. Most importantly, a triangulation approach may help to generate further understanding from the data produced by research (O'Cathain, Murphy and Nicholl 2010) and provides the motivation for the qualitative process evaluations undertaken in the research approach.
The methods chosen in this thesis were selected for their appropriateness in answering the research questions developed by each research study. Publication One utilised a systematic review and meta-analysis method to assess current published literature describing the establishment of care pathways in primary care settings. In publication Two, a focus group series was undertaken to gain views and perspectives of a target population, utilising Actor Network Theory as a way of providing a theoretical

perspective for the analysis. Publication Three utilised a stated preference method and enhance participant involvement in care pathway design. Publication Three employed the econometric method, a discrete choice experiment, which utilises a standard questionnaire describing different choices and asks participant to choose which option they prefer. Publication Four utilised a quasi-experimental approach to managing quantitative data generated from a testing pilot for blood borne viruses. This study evaluated the ability of pharmacies to offer blood borne virus testing and utilised a logic model to guide a process evaluation based around normalisation process theory. Publication Five utilised a cluster randomised controlled trial to test the feasibility of the care pathway that had been developed; an extension to the process evaluation was undertaken and a comparison of pathway costs was mapped for both the intervention and conventional pathways. Publication Six is a protocol for a definitive multi-centre cluster randomised controlled trial and Publication Seven is the full enactment of this protocol after implementation and delivery. The multi-centre cluster randomised controlled trial also contains an economic analysis and post implementation process evaluation of staff views and perspectives. Publication Eight is a qualitative synthesis of the results gained from the previous process evaluation work undertaken in the programme, using a complexity approach to suggest causal relationships underlying the operation of the care pathway. The use of these different techniques to triangulate knowledge is consistent with the iterative approach to the development of understanding in how an intervention performs in the real world, as suggested by the MRC guidance (Craig, Dieppe et al 2008)

2.7.1 Systematic Reviews and Meta-analysis

A systematic review is a method for identifying and assessing all relevant research on a specific topic, using all available sources and employing a pre-determined method. Systematic reviews may be conceptualised as following five stages: Framing the question; identifying relevant publications; assessing study quality; summarising the evidence; interpreting the findings (Khan, Kunz et al 2003). The data collected in a systematic review can be observational or experimental and be synthesized by narrative synthesis and by meta-analysis. Systematic reviews can be used to help resolve inconsistencies and controversies in the evidence base. Meta-analysis is a statistical technique for combining data from separate studies to provide a pooled estimate of the outcome of interest. The pooled analysis can provide an indication of the size of effect associated with an intervention (Popay, Roberts et al 2006).

Limitations of systematic reviews include the difficulty of identifying all relevant publications. There are numerous ways in which bias can be introduced into reviews and meta-analyses. Inferior methodological quality of included trials may result in the findings of reviews of study outcomes being compromised. Publication bias can distort findings since trials with positive results are more likely to get published, than trials that do not deliver a significant outcome. Among published studies, those with significant results are more likely to get published in English and are more likely to be cited and so be more readily identified. Positive findings are more likely to be published more than once which means that they will also be more likely to be identified and included in a systematic literature search. Studies tend to report the most favourable findings, which can result in bias. Criteria for inclusion of studies (PICOS) into a review may be influenced by knowledge of the literature by the researchers (Eggar, Davey-Smith and Altman 2007).

However, since systematic reviews are more likely to avoid bias than traditional, narrative reviews, this method was employed in this research programme. The emergent nature of studies of care pathways using direct-acting antiviral medication in community and primary Several of the studies were also only available as conference abstracts. The opportunity to use assessment of bias and strength of evidence techniques within the study provided some assurance that the analysis of the evidence base was rigorous and trustworthy.

2.7.2 Focus Groups

Focus groups are a qualitative method of gathering data on what people think or feel about an issue, a product or a service. Participants are selected because they have certain characteristics in common that are important in delivering the topic of interest being discussed in the focus group. Focus groups have a number of strengths and weaknesses that distinguishes them from other qualitative methodologies. The use of this method has its origins within the fields of social science and market research. In a good quality focus group, the researcher takes on a less dominant and directing role than in an interview approach and respondents can comment on areas considered by them to be most important. Group reactions can be gauged to new ideas and group brainstorming can be prompted.

Focus groups explicitly use group interactions as part of a controlled group discussion to generate data. Focus groups can be viewed as performances in which participants jointly produce accounts about a proposed topic in a socially organised situation and in which

both the facilitator and the participants share an assumption about the purpose of the discussion (Smithson 2000). The quality of the outcomes produced is dependent on the use of systematic procedures for data collection, data handling and data analysis and also on researcher neutrality. Questions should be piloted to ensure that they are understood and the conditions that the group discussion is undertaken in need to facilitate open sharing.

The findings of focus groups may be distorted by the presence of dominant voices and opinions. Such influences can be ameliorated through purposefully making the structure of the groups homogeneous for sex, age, education and current occupational position. However, such plans may be limited by the lack of influence on which participants attend the sessions. The facilitator can also contribute to the management of this effect, through attempting to balance contributions to the discussion and by encouraging quieter members of the focus group participants to express a viewpoint. Since the unit of analysis of a focus group is said to be the collective voice, analysis recognises the existence of already-held opinions within the group, plus the formation of a collective consensus through the process of group discussion: a normative discourse (Smithson 2000). The effect of the facilitator may influence the outputs from the group discussion. It may be considered that a facilitator from the same cultural background as the participants may improve the quality of facilitation and interpretation of the discourse. Considerations of this effect may be countered both by promoting the independence of the facilitator and also acknowledging reflexivity and self-awareness (Raheim, Magnussen et al 2016).

2.2.3 Semi-Structured Interviews

Semi-structured interviews are a qualitative method of eliciting views and perceptions on a topic and are conducted conventionally with a single participant who is asked a series of closed and open-ended questions, often accompanied by supplementary more probing questions looking to elicit further explanations (Newcomer, Hatry and Wholey 2015). The interviews may be conducted with the support of a topic guide which acts as a tool to aid the progress and scope of the interview. Such topic guides support a systematic approach to data collection, data handling and analysis and enable a justification to be incorporated into the documentation for each question that is asked of the participant. Interviews are an intrusion into the participants' private life, both in terms of time spent and the disturbance of questioning.

Semi-structured interviews have a number of advantages and disadvantages over other qualitative methods. They enable independent contributions from an individual that are

distinct from those of group. Probing open-ended questions can elicit a range of candid responses that may not be offered in the company of a focus group. Such interviews can reduce incomplete answers, can approach a topic systematically and yet can be flexible enough to accommodate unexpected responses.

However, the interviewer may have pre-conceived ideas and expectations about the topic which may introduce bias into the data collection, even if this is an unconscious effect. Such interviews are useful in a process evaluation where formative views are sought about the realist questions surrounding an intervention – "what works, for whom and in what circumstances?" (Pawson and Tilley 1991). However, the planning, implementation and analysis of a semi-structured interview series is resource intensive and requires that the interviewer has well developed skills and is insightful about both the subject matter and also the potential sensitivities of participants (Alshenqeeti 2014)

2.2.4 Discrete Choice Experiments

Discrete choice experiments are a stated preference technique used in health economics. In this method, the researcher constructs a series of alternative choices based on a limited number of important attributes that describe a service, a product or an issue and administers as a questionnaire (Stirling and Dolan 2004). Respondents choose from these alternative options for the choice series, which have different levels of the attributes, in order to infer the relative weighting attached to each level that has been assigned. Discrete choice experiments can be used to calculate the health gains available from different interventions, where the various dimensions of health are used as attributes; calculate the implied willingness to pay (willingness to wait) for those attributes where a value is included; express the relative value of different attributes, including non-health outcomes and process factors, in comparison to each other (de Bekker-Grob, Ryan and Gerard 2010). Discrete choice experiments assume that the value of a product or service is based on the sum of its attributes and that an individual's valuation and preference is dependent on the relative levels of these attributes.

Discrete choice experiments have a series of implementation issues that should be acknowledged when using this method: the approach seeks to identify normative values, but thought should be given to the generalisability of the values identified (Reed Johnson, Lancsar et al 2013). There are a range of psychological issues that should be addressed including the cognitive burden of the questionnaire, the potential for hypothetical bias and framing effects from the way that the questionnaire is written. Technical issues also arise

when considering the sample size of scenarios, as representative from the full range of possible combinations (Reed Johnson, Lancsar et al 2013).

2.2.5 Quasi Experimental Designs

A central task of all research designed to evaluate causation is the approximation of what did happen compared to what would have happened, if the intervention or event had not occurred (Shadish, Cook and Campbell 2002). A quasi-experimental evaluation is one in which the units of interest are not assigned to conditions randomly, but an attempt is still made to test the counterfactual hypothesis of what did happen compared to what would have happened. In these research designs, units are often people, time periods or institutions. Quasi-experimental design involves selecting groups, upon which a variable is tested, without any random pre-selection processes. After selection, the experiment proceeds in a very similar way to any other experiment, with a variable being compared between different groups, or over a period of time. The quasi-experimental approach is often convenient and, and for feasibility work, implementation is rapid to deliver and causes little disruption in situations where services are being provided.

This inherent weakness in the methodology does not undermine the validity of the data, as long as they are recognized and allowed for during the whole experimental process. Quasi experiments resemble quantitative experiments, but the lack of random allocation of groups or proper controls, means that statistical analysis is more limited.

In quasi-experiments, the cause of investigation is manipulable and occurs before the effect is measured. Since quasi-experimental control groups are not randomly assigned, they may differ from the intervention group in many systematic ways. The variance incorporated into such designs could theoretically provide plausible alternate explanations for the outcomes that are identified. Investigators may be prone to report the results more enthusiastically for quasi-experiments than for randomised studies. The risk of investigator bias is therefore a further limitation (Kim, Nitsch, Wang and Bakhai 2006). Quasi-experimental approaches therefore provide less compelling support for inferences that are drawn from them (Craig, Cooper et al 2012).

2.2.6 Cluster Randomised Controlled Trials

In conventional randomised experimental designs, individual participants are randomly allocated to the intervention of interest or a control. In cluster randomised designs, a group of individuals, a hospital or even a community is utilised as the unit of randomisation. Cluster designs are particularly useful in health care setting where patients are nested within larger group settings (Mallick, Bakhai et al 2006) and patients

in one cluster may be more likely to have similar outcomes. The cluster design has advantages when patients or clinicians may contaminate the intervention effect because of exchange of information within the cluster. The cluster approach is useful for evaluating quality improvement strategies in healthcare interventions.

In cluster randomised trials, statistical power is reduced in comparison to similarly sized conventional randomised designs. Sample size calculations are therefore inflated using a cluster inflation factor to accommodate for the clustering. Although the unit of randomisation is the cluster, the unit of reporting is at the patient level. A statistical adjustment is made to adjust for the cluster size and number of clusters, as well as how closely related patient outcomes are within a cluster (intra-cluster correlation coefficient). The design effect indicates the amount by which the sample needs to be inflated. A large design effect number requires more subjects than a conventional randomised trial design (Rutterford, Copas and Eldridge 2015).

In the analysis of cluster randomised trials, failure to control for the correlation between individuals in the same cluster can lead to bias, over-estimating the treatment effect and increasing the chances of type one error; rejection of the null hypothesis (Hahn, Puffer et al, 2005). The CONSORT (Consolidated Standards of Reporting Trials) guidance now takes account of the special features of cluster designs and requires a statement of the rational for the Cluster Effect for design and analysis of utilising a cluster design and acknowledgement of the implications (Campbell, Elbourne et al 2004). In addition, the ethical issue surrounding the way being part of a cluster impinges on a study participant's latitude to consent independently has been raised. Other ethical issues such as the quality of scientific design and analysis, individual balance of risk and benefit especially for vulnerable patients, liberty to leave the study and the ability to exclude participants may also require consideration (Weijer, Grimshaw et al2011)

2.2.7 Systems Thinking Approaches

A systems thinking approach can be a useful way of considering the nature of the complex adaptive systems seen in health services. Such an approach takes a wider perspective, considering interaction effects, feedback loops and emergence within the larger system (Carey, Malbon, et al 2015). This approach was developed from a system dynamic theoretical frame stance which aims to underpin the mechanisms driving dynamic behaviour by identifying causal relationships, feedback loops, delays and unintended consequences. Causal loop diagramming is a tool used to analyse complex systems. It is a qualitative visual aid used to communicate assumptions about a dynamic

system (Belue, Carmack, et al 2012). Visualizing complex adaptive systems can enable a better understanding of the behaviour of the system and its agents. A specific function of the tool is to elucidate feedback loops (Cavana and Mares 2004). . Use of such visualizations can be used to generate hypotheses which feed into theory-driven evaluation and exploration of potential causal mechanisms and routes to improvement (Renmans, Holvoet and Criel, 2015).

CHAPTER 3:

DELIVERING HEPATITIS C TESTING AND TREATMENT IN COMMUNITY AND PRIMARY CARE SETTINGS

Content

The chapter comprises the paper Radley A, Robinson E, Aspinall EJ, Angus K, Tan L, Dillon JF. A systematic review and meta-analysis of community and primary-care-based hepatitis C testing and treatment services that employ direct acting antiviral drug treatments – (BMC Health Service Research 2019; 19:765). Radley conceived and wrote the first and subsequent drafts of the paper with clinical guidance from Dillon; Radley, Tan and Angus contributed to the review's literature search, screening and data extraction. Robinson, Aspinall and Radley contributed to the meta-analysis and interpretation. All co-authors read and commented on the first drafts of the paper and approved the final version.

Evidence Contributions

The paper reports the results of Radley et al (2019): A systematic review and meta-analysis of community and primary-care-based hepatitis C testing and treatment services that employ direct acting antiviral drug treatments. The paper provides an overview of the evidence base, describing the published evaluations of care pathways that offer the newly introduced Direct Acting Antiviral (DAA) medicines into community and primary care environments. It reports the results of an updated systematic literature and meta-analysis of the first studies to be published after the marketing of these medicines in 2013. The World Health Organisation Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection promote simplified service delivery models; integration with other services; decentralised services supported by task-sharing and community engagement to address stigma and increase reach. Previous medicines regimens used to treat HCV required intensive medical support and monitoring because of the heavy treatment burden and adverse effects associated with these drugs. The consequences of this were that treatment was usually supervised by specialist medical teams in secondary care environments to ensure safety, but also that the target population – people who inject drugs – did not easily access the care provided, through a number of explanatory factors set out in Chapter 1. Inertia in these established systems was

recognised by the Guidelines, which sought to overcome many of the barriers preventing the main group of people with HCV infection receiving curative treatment.

Knowledge Translation Contributions

The systematic review provides support for the development of an effective pharmacy-based care pathway for testing and treatment of HCV. The evidence assessed provides detailed knowledge of the range of pathways that have been established and evaluated, as well as the types of evaluations that have been undertaken. The objectives of these evaluations, to link people into care; to carry out testing for BBVs; to establish them on treatment; to support them to complete treatment and to measure the achievement of a clinical cure (SVR) are fundamental in relating the work undertaken in this research programme to established literature.

In addition, Radley has provided evidential support to the development of the report entitled *Recommendations on hepatitis c virus case-finding and access to care: Report of the national short-life working group* (August 2018), requested by the Scottish Government and undertaken through the Scottish Health Protection Network. The findings of the systematic review and meta-analysis have been presented by invitation, to a series of national and international conferences on care and treatment of people with HCV infection.

3.1 A systematic review and meta-analysis of community and primary-care-based hepatitis C testing and treatment services that employ direct acting antiviral drug treatments

The following paper is a verbatim copy of Radley A, Robinson E, Aspinall EA, Angus K, Tan L, Dillon JF published at BMC Health Services Research 2019 (19) 765
https://doi.org/10.1186/s12913-019-4635-7

ABSTRACT

Background: Direct Acting Antiviral (DAAs) drugs have a much lower burden of treatment and monitoring requirements than regimens containing interferon and ribavirin, and a much higher efficacy in treating hepatitis C (HCV). These characteristics mean that initiating treatment and obtaining a virological cure (Sustained Viral response, SVR) on completion of treatment, in non-specialist environments should be feasible. We investigated the English-language literature evaluating community and primary care-based pathways using DAAs to treat HCV infection.

Methods: Databases (Cinahl; Embase; Medline; PsycINFO; PubMed) were searched for studies of treatment with DAAs in non-specialist settings to achieve SVR. Relevant studies were identified including those containing a comparison between a community and specialist services where available. A narrative synthesis and linked meta-analysis were performed on suitable studies with a strength of evidence assessment (GRADE).

Results: Seventeen studies fulfilled the inclusion criteria: five from Australia; two from Canada; two from UK and eight from USA. Seven studies demonstrated use of DAAs in primary care environments; four studies evaluated integrated systems linking specialists with primary care providers; three studies evaluated services in locations providing care to people who inject drugs; two studies evaluated delivery in pharmacies; and one evaluated delivery through telemedicine. Sixteen studies recorded treatment uptake. Patient numbers varied from around 60 participants with pathway studies to several thousand in two large database studies. Most studies recruited less than 500 patients. Five studies reported reduced SVR rates from an intention-to-treat analysis perspective because of loss to follow-up before the final confirmatory SVR test. GRADE assessments were made for uptake of HCV treatment (medium); completion of HCV treatment (low) and achievement of SVR at 12 weeks (medium).

Conclusion: Services sited in community settings are feasible and can deliver increased uptake of treatment. Such clinics are able to demonstrate similar SVR rates to published

studies and real-world clinics in secondary care. Stronger study designs are needed to confirm the precision of effect size seen in current studies. Prospero: CRD42017069873

BACKGROUND

Of the 71 million persons infected with HCV, 5.6 million (8%) currently inject drugs [1, 2]. The World Health Organization (WHO) has defined global targets for HCV diagnosis and treatment, which represents a major step towards the aim of global elimination by 2030 [3].

However, rates of uptake of HCV testing, linkage to care and treatment remain low across many countries [4]. Barriers to accessing funded Direct Acting Antiviral (DAA) drug treatment may be due to provider concerns regarding co-morbidities, adherence, and side effects management [5]. Social factors affecting treatment access have been categorised as social stigma, housing, criminalisation, health care providers' attitudes and stigmatising practices, and gender [6]. Individuals may prioritise other needs and may be wary of the consequences of a diagnosis on their circumstances; health systems may present complex and rigid arrangements that must be navigated in order to access care [7]. The stigma associated with both injecting drug use and HCV infection is pervasive [8]. The concept of the care cascade has focussed attention on the performance of different pathways and the attrition of patients accessing testing, diagnosis, treatment and care [9].

It is common in many developed and developing countries, for specialist clinicians to provide HCV treatment, often from hospital outpatient facilities [10]. Recently, prescribing of DAAs has become common practice in many countries [10]. Treatment of HCV with these medicines is simple and well-tolerated [11]. The safety profile and high efficacy of DAAs means that HCV treatment can be delivered by a range of non-specialist clinicians including nurses, pharmacists and general practitioners, therefore providing enhanced access to virological cure (SVR). [12]. The ease of transferring care to community and primary care environments is assisted by the use of treatment regimens that do not contain ribavirin or interferon [13]. Progress with implementing treatment pathways provided by non-specialists in community and primary care environments has been identified as one of the key steps in the elimination of HCV [14]. The World Health Organization's Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection promote simplified service delivery models: integration with other services; decentralised services supported by task-sharing; and community engagement, with the intention of reducing stigma and increase uptake of treatment [14].

This review was undertaken to identify rates of treatment uptake, treatment completion and achievement of sustained viral response for adults infected with hepatitis C using DAA-only treatment regimens in community and primary care-based care pathways, evaluated by studies using observational and experimental study designs. Studies that compared community-based treatment care pathways with specialist care were actively sought.

METHODS

This systematic review was undertaken and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15]. The methods of analysis and defined inclusion criteria were specified in advance and documented in a study protocol. The study was registered in PROSPERO (CRD42017069873). The PICOS elements defined for this review are set out in Table1 The rationale adopted in the design of the PICOS elements was intended to provide some answers to the questions raised by the WHO Guidance and its recommendations for simplified and decentralised treatment delivery models, integrated with other services in community and primary-care environments [14]. Therefore a population over 18 years old was selected, as being less likely to have gained their infection through vertical transmission. Co-infected individuals with other blood borne virus infections were also excluded as their care was likely to be more complex, requiring specialist rather than simplified care. Studies from prison populations were excluded since these individuals lived in contained communities. Studies that utilised interferon and ribavirin-based treatment regimes as the primary intervention were also excluded, since monitoring and patient management requirements, made simplified and decentralised care less likely. Sustained viral response at 12 weeks (SVR12) was taken as a marker for virological cure; failure to achieve SVR may be attributed to both treatment failure and loss to follow-up [16]. Studies were restricted to the English language since study resources precluded any translation activities. Published studies were utilised including conference abstracts, in order to capture results from early studies when the first DAAs were introduced into practice.

Search strategy

Published research was identified by formal searches of five electronic databases (Cinahl, Embase, Medline, PsycINFO, PubMed) from January 2013 to December 2017, as well as Google Scholar. The last search was run on 11 December 2017. Search topics included "hepatitis C", "treatment" and "setting". A comprehensive list of search terms related to

each of the search topics was used to develop a search strategy for each electronic database. Search strings were formulated by using a combination of keywords and indexed subject headings (MeSH and EMTREE terms). Primary care was defined using the WHO accepted terminology that promotes Primary Care as a key process in the health system: "it is first-contact, accessible, continued, comprehensive and coordinated care" [17] and community environments being the geographical locations where groups of people live.

The full search strategy is set out in supplementary file 1. Reference lists of selected articles, citing articles and relevant review articles retrieved during the initial search were hand-searched and forward citation checks were undertaken to identify any additional studies. Abstracts from the selected scientific conferences were screened for review eligibility.

Study selection

Data retrieved through the study search strategy were imported into EndNote X8 (Thomson Reuters, New York, NY, USA) and any duplicates removed. Titles obtained from the initial search strategy were screened and irrelevant citations were removed. Abstracts were then assessed using the inclusion and exclusion criteria by two reviewers independently (AR and LT) to establish a relevant pool of evidence for further evaluation. Full-texts from all abstracts identified for further evaluation and were double-screened independently by the two reviewers to assess whether they met the defined inclusion and exclusion criteria. In the event of a disagreement, the senior investigator (JFD) determined final inclusion. The lead author contacted conference abstract authors to attempt to obtain further study results if available. Studies published from identified conference abstracts were screened for review.

Data collection process and data items collected

Data from studies included for analysis were extracted by the lead author (AR) using a standardised data extraction form (Microsoft Excel 2010 Redmond, WA, USA). A second reviewer (ER) also independently assessed the extracted data, and disagreements were resolved by discussion until consensus was reached. The following variables were documented: first author, title, publication year, study design, study location, setting, intervention description, comparator description, sample size outcome description and number of participants achieving SVR12 (and percentage if applicable).

Risk of bias assessment in individual studies

The risk of bias in individual studies was assessed by two reviewers (AR and ER) using the Cochrane Collaboration's risk of bias tool for randomised studies [18] and the "Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses" [19]. For randomised studies, these outcomes were evaluated along the six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. The domains deemed as 'high risk' of bias for each study per outcome were determined. Outcomes for the non-randomised studies were evaluated along seven domains: bias due to confounding; bias in selection of participants into study; bias in classification of interventions; bias due to deviations from intended interventions; bias due to missing data; bias in measurement of outcomes; and bias in selection of the reported result. The overall risk of bias for these studies was classified into five categories: low risk of bias; moderate risk of bias; serious risk of bias; critical risk of bias or no information.

The NOS scale measures three items: selection of cases and controls including their definition and representativeness; comparability of cases and controls in design and analysis; and exposure ascertainment. The scale has a minimum score of 0 and a maximum score of 9. Risk of bias was rated as high, medium or low according to the scores obtained by reviewing the selection, comparator and exposure categories. Risk of bias was rated low if studies scored 8 or 9; medium risk if studies were scored as 6 or 7. Studies were rated as having a high risk of bias if they were scored as having 5 or less or scored zero for the comparator category [20].

We assessed the strength of evidence using GRADE [21]. The scheme evaluates a required group of domains (study limitations, directness, consistency, precision and reporting bias) and enables grading of the strength of evidence as High; Moderate; Low or Insufficient. Use of this approach enabled us to summarise the outcomes and findings and make clear judgements about the effects of the interventions.

Data analysis

The characteristics and findings of the studies included were summarised and structured using tables. Studies evaluating similar service environments in community and primary care-settings were grouped together to facilitate comparison.

Study designs, participants, interventions and reported outcomes varied significantly, and a meta-analysis was unable to be performed on all included studies. Studies were excluded from the meta-analysis if the reviewers considered them to be sufficiently flawed so as not to contribute meaningfully to the body of evidence [21].

The characteristics and findings of included studies amenable to meta-analysis were summarised using tables and forest plots. Risk ratio (RR) and corresponding 95% confidence interval (95% CI) was calculated for each study outcome, using the initial number of eligible participants included and the number achieving the outcome of interest in each arm. Analyses were conducted using statistical package Stata v14.0 (College Station, TX, USA).

Data synthesis

Deriving Pooled Estimates of treatment uptake, treatment completion and SVR

Treatment uptake, treatment completion and SVR and their exact 95% confidence intervals (CIs) were calculated assuming a binomial distribution. Pooled estimates were derived using random- or fixed-effects methods, according to whether significant heterogeneity (defined as $I^2 > 30\%$) was or was not present, respectively. Sensitivity analysis was used to assess the impact of study quality (restricting to studies with an NOS score ≥6) on the pooled estimate of SVR.

Further sensitivity analysis was used to assess the impact of conference abstracts on the pooled estimate of SVR. We identified studies using similar environments from which to deliver care and grouped them into categories. Factors identified as linking studies within categories were examined as well as factors that differentiated studies from each other.

RESULTS

Study Selection

The searches yielded 9,137 publications after removal of duplicates (Figure 1). This resulted in 121 articles retrieved for full text inspection and 17 included for analysis. Explanations for exclusion of studies at the full text stage are provided in Figure 1. These included: did not fulfil inclusion criteria; no treatment intervention; review or opinion article; other (e.g. insufficient detail reported in conference abstract).

Study characteristics

Studies evaluated care pathways in primary care [22, 23, 24, 25, 26, 27, 28]; in integrated health systems (Extension for Community Healthcare Outcomes, ECHO) [29, 30, 31, 32]; in opioid treatment centres [33, 34, 35]; in pharmacies/pharmacist clinics [36, 37] and by telemedicine [38]. Characteristics and findings of included studies are set out in Table 2. These studies originated from United States of America (8); Australia (5); United Kingdom (2); and Canada (2). The number of identified studies published as conference abstracts reflected the length of time that DAAs have been widely available outside specialist environments. Six from seventeen studies were only available as conference

abstracts. There were two randomised controlled trials, four cohort studies, nine retrospective data analyses and two prospective non-experimental designs. All were conducted on populations at high risk of HCV infection, such as people who inject drugs and people on Opioid Substitution Therapy (OST) programmes. Table 3 describes the outcomes from the meta-analysis of selected studies and Table 4 defines the Strength of Evidence Assessment for identified studies answering the PRISMA objective. Details of assessment of bias and design for studies are located in Supplementary Table 1 (non-randomised) and Supplementary Table 2 (randomised)).

Primary Care

Seven studies evaluated interventions to enhance treatment uptake and achievement of SVR in primary care environments [22, 23, 24, 25, 26, 27, 28]. One study was a randomised controlled trial (RCT), two were cohort studies and four were non-randomised studies. Four studies utilised nurses in delivery of the care pathway. Three studies included uptake of testing and assessment in their description of care and all the studies discussed uptake of treatment and ascertainment of SVR. The RCT reported a significant difference between those commencing treatment in primary care arm than in the Standard of Care arm (SOC) (75% Vs 34%, $p<0.001$) and proportion gaining an SVR12 was significantly higher in the primary care arm than in the SOC arm (49% vs 34%, $p=0.043$).

Two studies reported a reduction in potential SVR rates because of failure of participants to complete the confirmatory blood test at 12 weeks after completion of DAA treatment. All studies reported increased access to treatment in primary care environments and high rates of SVR attainment.

Integrated Health Systems (ECHO)

Four studies provided evaluations of care through integration of specialist centres with primary care delivery [29, 30, 31, 32]. One study was a retrospective cohort study and three were non-randomised studies. Three of the four studies utilised the "ECHO" care pathway in which hepatitis specialists support primary care providers through video-conferencing and collaboration on specific cases, with a defined curriculum and active mentorship [39]. None of the studies discussed uptake of testing amongst their treated cohorts. All studies increased access to treatment and high rates of attainment of SVR.

Opioid Treatment Centres

Three studies evaluated care provision in dedicated setting where people with opioid addiction received harm reduction and treatment services [33, 34, 35]. All three studies

were non-randomised analyses of treatment data and assessed the uptake and completion of treatment by participants using these services. No assessment of the extent of testing of these populations was discussed. All studies reported high rates of treatment uptake and treatment completion in diagnosed individuals. These studies all described problems with retention of participants in the service post-treatment with consequent reductions in uptake of confirmatory SVR testing.

Pharmacies / Pharmacist Clinics

Two studies evaluated hepatitis C care provision by pharmacists in community and primary care settings [36, 37]. One study was a feasibility RCT that compared the delivery of a community pharmacy test and treatment pathway with standard hospital-based care. One study was a non-randomised data analysis. The RCT demonstrated an increase in testing uptake, when the participant received all care in a pharmacy environment and showed increased retention in care. Data from this study also demonstrates a marked loss of patients from the care pathway when they were asked to attend the local hospital. The non-randomised study concluded that patients treated in pharmacist clinics achieve high rates of SVR similar to non-pharmacist clinics

Telemedicine

A single cohort database study [38] compared treatment uptake and SVR rates in participants cared for through a telemedicine pathway (n=157) with participants cared for through a standard care pathway (n=1,130). The study demonstrated increased access to care form under-served and remote areas and concluded that the telemedicine intervention achieved high rates of treatment initiation and SVR.

Data synthesis

The 12 studies eligible for meta-analysis examined treatment uptake, completion and SVR in a variety of primary care environments; integrated systems (ECHO) that linked specialists with primary care providers; opioid treatment centres; pharmacies / pharmacist clinics; telemedicine and specialist hospital care. The remaining five studies were unsuitable for meta-analysis due to non-reporting of the required outcomes, use of Pegylated interferon or insufficient time to achieve SVR. Across the 12 studies, the pooled estimate is shown in Supplementary Table 3. Forest plots for suitable studies are set out in Figures 2, Figure 3 and Figure 4. These plots demonstrate that across the variety of community and primary care environments, a consistent direction of effect to improve treatment uptake, treatment completion and achievement of SVR is seen.

Greater uptake was seen for the Primary Care and Pharmacy Locations, compared to the Specialist Care Location and comparable SVR rates were demonstrated (Table 2).

In this analysis, heterogeneity was noted to be high so a sensitivity analysis restricting to higher-quality studies (NOS score ≥6) was performed. Despite this the heterogeneity remained high. A further sensitivity analysis was performed restricting the meta-analysis to published studies only. See Supplementary Table 2 in the appendix. This had no impact on heterogeneity.

DISCUSSION

This paper reviews evaluations of care pathways that utilise DAAs in a range of community and primary care settings. The WHO Guidelines on care and treatment of persons diagnosed with chronic HCV infection promote simplified service delivery models; integration with other services; decentralised services supported by task-sharing; and community engagement to address stigma and increase reach [14]. The studies considered in this systematic review and meta-analysis therefore provide some evidence for the extent of implementation of these guidelines.

The studies identified that met our inclusion criteria were grouped according to location: primary care; integrated health care systems (ECHO); opioid treatment centres; in pharmacies / pharmacist clinics; and through telemedicine. These care pathways acknowledged the need to provide local services with reach into the communities where people with hepatitis C live their lives.

In all three areas assessed in our study: uptake of treatment; completion of treatment; and attainment of SVR, a positive outcome was reported by all identified studies. This was seen across each of the distinct environments from which the care was provided. Since the positive outcomes were drawn from distinctly different pathways of care, further confidence might be inferred from this consistency of direction of effect . However, amongst the studies that met our inclusion criteria, there was a lack of studies using comparators from specialist centres. Data contained in these studies nevertheless demonstrated high uptake of treatment and high rates of attainment of SVR: among populations of vulnerable people who normally struggle to access care. Studies that did include comparators showed no significant differences in uptake or SVR. Several of the studies reported an increased uptake of treatment, but most reported equivalence. Some studies reported lower rates of attainment of SVR, because of study participants failing to undergo a confirmatory blood test post-treatment, within the study timelines. With DAAs

SVR rates of greater than 97% are delivered if patients adhere to treatment, therefore completion of therapy can be a surrogate for SVR [16].

Previous systematic reviews have considered barriers and facilitators to care, as well as the views and experiences of people who inject drugs [7, 40]. These studies concluded that the target groups for HCV often had poor levels of knowledge about the infection and of the processes involved with testing and treatment. A fear of stigma and discrimination and a reticence to discuss risk behaviours tended to prevent engagement. These barriers could be addressed through educating participants, increasing awareness and redress of institutionalised stigma and integrating HCV treatment pathways into other services where the target group were likely to go.

Increased uptake of testing has been observed when testing is offered at the same time as other routine care [4]; with integrated services for both opioid users and with mental health services. There are advantages to targeting services at populations with predicted high prevalence of HCV [41]. Provision of HCV treatment as part of a directly observed treatment arrangement, increased attainment of SVR [42]. Achievement of these factors within local health systems needs to be commonplace if the WHO target for elimination is to be met [43]. There is some evidence that this is now happening [44].

The results from this systematic review highlight the lack of well-controlled randomised controlled trials and comparative studies, with just two randomised controlled trials identified and four cohort studies. While the publication of such studies is an important step in building confidence that decentralisation of hepatitis C treatment can be accomplished, the paucity of evidence reflects the difficulty in funding pathways to care studies and the relatively recent removal of the restrictions on the use of DAAs. Two further studies have been commenced identify that further evaluations of interferon-free treatments in primary care environments are underway [45, 46].

As with most systematic reviews, the quality of the studies and the heterogeneity of the study populations included in the analysis present a limitation of this study. The sensitivity analyses performed for our analysis did not have an impact on heterogeneity, meaning that an unexplained source of heterogeneity may be present. These difficulties may reflect the variety of ways in which patients can access HCV treatment. This may be positive and may be explained by the development of more patient centred pathways. These factors prevented a meta-analysis being achieved for many of the studies identified as eligible through the PICOS question defined for this review. Many of the studies that met the inclusion criteria were only available as conference abstracts at the time of review, including one of the randomised controlled trials.

Nevertheless, over 10,000 participants were included in the identified studies. All studies had a consistent direction of effect, providing optimism that future evaluations will confirm with precision the effect size that should be delivered by simplifying treatment pathways and decentralising them to primary care. In terms of further limitations, we acknowledge limitations in the chosen methods for the systematic review, including potential publication bias to the findings by excluding non-English language studies; or any other biases introduced by our chosen inclusion and exclusion criteria.

CONCLUSION

This systematic review and meta-analysis identified studies which demonstrate the feasibility of decentralising care and providing local services with reach into communities of people infected with HCV. Such pathways may increase uptake of treatment and can provide sustained viral responses equivalent to those attained in specialist centres. Further studies are needed to confirm the promising start to the implementation of interferon-free treatment regimens. The successful implementation of such pathways to deliver successful patient outcomes is a key requirement for a "treatment as prevention" strategy as a pathway to elimination of HCV [47].

The references to this manuscript are provided in Appendix 9.1

Abbreviations

Direct Acting Antiviral	DAA
Grading of Recommendations Assessment, Development and Evaluation	GRADE
Hepatitis C	HCV
Human Immunodeficiency Virus	HIV
Newcastle Ottawa Scale	NOS
Opioid Substitution Therapy	OST
Population; Intervention; Comparison; Outcome; Study Design	PICOS
Preferred Reporting Items for Systematic Reviews and Mata-Analysis	PRISMA
People Who Inject Drugs	PWID
Randomised Controlled Trial	RCT
Risk Ratio	RR
Standard of Care	SOC
Sustained Viral Response	SVR
Sustained Viral response at 12 weeks	SVR12
World Health Organization	WHO

Table 1: Elements of the PICOS question defined for this review

	Inclusion	Exclusion
Population	Age 18 years and over Infected with hepatitis C	Age less than 18 years Co-infection with Hepatitis B virus Co-infection with Human Immunodeficiency Virus
Intervention	Provision of hepatitis C treatment in any primary care and community environments Treatment using any direct acting antiviral therapy Care provider could be any health care provider	Hepatitis C treatment in prison populations Treatment with ribavirin / interferon regimes as the primary intervention
Comparison	Care in any hospital or secondary care environment or no comparison group	
Outcome	Treatment uptake, treatment completion and Sustained Viral Response outcomes	
Study design	Observational studies, retrospective or prospective cohort studies, randomised trials; conference abstracts; qualitative and mixed methods studies	Case studies; systematic reviews

Table 2: Characteristics and findings of included studies

Care Location	Year	Country	Design	Intervention	Comparator	Number of participants	Uptake (%)	Sustained Viral Response (SVR) (%)
Primary Care								
Bloom	2017	Australia	Prospective cohort study of treatment uptake and SVR	Adherence to Direct Acting Antiral treatment protocols	Treatment by tertiary care provider	1044	503 (40.6)	253 (50.2)
Francheville	2017	Canada	Prospective observational study design	Specialist nurse-led care	No comparator group	242	93(38.4)	82(88.2)
Kattakuzhy	2017	USA	Non-randomised open label study	Treatment by primary care providers (PCP) and nurse practitioners (NP)	Standard care - Treatment by secondary care clinic	NP 150 PCP 160		NP 134(89.3) PCP139(86.9)

McCLure	2017	Australia	Retrospective data analysis of SVR	Nurse-led care and GP remote consultation	Specialist care in Tertiary centre	Nurse-led 70	50(74.3)	46(65.7)
Miller	2016	USA	Retrospective observational study	Treatment by primary care providers	No comparator group	95		79(83)
Norton	2017	USA	Retrospective cohort study of SVR	Treatment in urban primary care centre	SVR 12 in PWIDs and non_PWIDs	89		85(95.5)
Wade	2018	Australia	Randomised controlled trial	Testing, assessment and treatment in primary care	Testing, assessment and treatment in tertiary care	59	31(52.5)	14(23.7)
Integrated Health Systems (ECHO)								
Abdulameer	2016	USA	Retrospective data analysis of SVR	VA-Echo model supporting primary care	No comparator group	588		318 (54)

				providers				
Beste	2017	USA	Retrospective cohort study of treatment uptake and SVR	VA-Echo model supporting primary care providers	Standard care - Treatment by unexposed primary care providers	6431	1303 (21.4)	(58.2)
Buchanan	2015	United Kingdom	Retrospective data analysis	Community-based outreach clinic	Standard care - Treatment by secondary care clinic	77	24 (31.2)	
Georgie	2016	USA	Retrospective data analysis of SVR	VA-Echo model supporting primary care providers	Treatment by sub-specialist providers	623		Genotype 1 (GT1) (99) GT2 (98) GT3 (79)
Opioid Treatment Centres								
Butner	2017	USA	Retrospective data analysis	Opioid treatment	No comparator group	75	75.0	64 (85.0)

				programme				
Morris	2017	Australia	Retrospective data analysis of treatment uptake and SVR	Treatment in a community-based harm reduction and treatment facility	No comparator group	127	122(96)	102(80.3)
Read	2017	Australia	Retrospective data analysis of SVR	Treatment of PWIDs in primary care setting	No comparator group	72		59(81.9)
Pharmacies / Pharmacist Clinics								
David	2017	USA	Retrospective data analysis of SVR	Pharmacy-managed clinics	Treatment by non-pharmacist providers	204		(83.6)
Radley	2017	United Kingdom	Pilot cluster RCT of treatment uptake and SVR	Treatment in community Pharmacy	Treatment by secondary care clinic	26	3(11.5)	3(11.5)

Telemedicine								
Cooper	2017	Canada	Retrospective cohort study of treatment uptake and SVR	Use of telemedicine	Treatment by secondary care clinic	157	35.0	18(11.5)

Table 3: Meta-analysis of studies examining treatment uptake, treatment completion and SVR among people with Hepatitis C treated in a variety of community settings or specialist hospital care

Abbreviations: CI, confidence interval; SVR, sustained virologic response a. Random-effects method used if $I^2 \geq 30\%$.

Inclusion Criteria	Treatment Uptake			Treatment Completion			SVR		
	No. Of studies	Heterogeneity (I^2)	Pooled estimate (95% CI)	No. Of studies	Heterogeneity (I^2)	Pooled estimate (95% CI)	No. Of studies	Heterogeneity (I^2)	Pooled estimate (95% CI)
Opioid Treatment Centres				2	77.7%	91.9 (82.2-100)	3	0.0%	82.3 (77.8-86.8)
Integrated Health System (ECHO)	1	Not applicable	75.6 (68.0-83.2)	1	Not applicable	96.8 (93.2-100)	2	84.6%	81.3 (66.9 - 95.5)
Telemedicine	1	Not applicable	22.3 (15.8-28.8)				1	Not applicable	51.4 (34.8-68.0)
Primary Care	1	Not applicable	67.4 (53.9 – 80.9)	1	Not applicable	100 (97.95-100)	5	94.9%	74.4 (60.3 – 88.5)
Pharmacies / Pharmacist Clinics	1	Not applicable	66.67 (58.3 – 75.1)				2	89.0%	79.0 (79.2 – 98.9)
Specialist Care	2	0.0%	34.5 (31.79 – 37.29)				5	96.8%	73.46 (60.9 – 85.9)

Table 4: Summary of key findings, outcomes and strength of evidence

Outcome	Study designs/ No. Studies	Findings and Direction of Effect	GRADE [21]
1. Uptake of HCV treatment	RCT – 2 Cohort – 3 Observational – 5	Two RCTs assessed as having low risk of bias reported a positive effect on uptake with precision and a consistent positive direction of effect. One cohort study assessed as having medium-grade study limitations also reported a positive effect on uptake.	Medium
2. Completion of Treatment	Cohort - 1 Observational - 2	One cohort study with medium study limitations reported a positive direction of effect on uptake.	Low
3. Sustained Viral Response (SVR) at 12 weeks (%)(SVR12)	RCT -2 Cohort - 4 Observational - 11	Two RCTs assessed as having low risk of bias reported a positive effect on SVR but were imprecise in the estimate of effect size. Four cohort studies and 11 observational studies with over 10,000 participants all reported a consistent positive direction of effect, but with significant study limitations.	Medium

3.2 Critical reflection

This systematic review and meta-analysis was undertaken in order to understand the breadth and quality of the literature supporting the World Health Organisation's guideline that delegation of hepatitis c testing and treatment services should be made to non-specialist practitioners in primary care settings and that elements of care should be delegate to the wider team. The circumstances making this possible are the introduction of a series of direct-acting antiviral (DAAs) drugs that have a small treatment burden and limited requirement for management and monitoring. The first DAA medicines were released in 2013, with widespread availability occurring around 2015. The high cost of these medicines (perhaps £30,000 per course) led to many administrations limiting their prescribing in order to manage the impact on medicines budgets. The advocacy undertaken by third sector organisations and interested academics supporting the case of people who use drugs (PWIDs) was therefore to make the case that decentralised care was feasible, desirable and effective. This study therefore was designed to critically evaluate the quality of evidence supporting this purpose.

3.2.1 Critique of methods

The methods used in this systematic review and meta-analysis are the same as those described in chapter two and set out in the paper, so an in-depth discussion of the strengths and weaknesses will not be repeated. As an overview, the study used a systematic approach to reviewing the evidence base, registering the structured research question (PICOS) on the PROSPERO database (https://www.crd.york.ac.uk/prospero/) and following the PRISMA guidance (http://www.prisma-statement.org/). The strengths of the review include the use of independent reviewers to screen all titles and abstracts identified by the database searches and the use of an independent researcher to agree any disagreements between reviewers. Decisions about study inclusion were agreed with an independent researcher and a thorough quality assessment was conducted for all studies. A meta-analysis was performed on a selection of included studies that were of sufficient quality and an estimate of direction of effect and effect size made for these studies. A strength of evidence assessment was performed on the group of studies to provide an overview of the research exercise.

As the study was conducted within finite time and resources, only papers in English were included and sources from grey literature were not identified. Independent double screening was split between two authors.

3.2.2 Critique of analysis

The relatively recent introduction of DAAs to clinical practice meant that studies identified from the database were often conference abstracts or reports of observational study designs and service developments. This fact is reflected in the poor performance of a number of included studies in the assessment of bias analysis and high study heterogeneity for some of the topics, meaning that a reduced number of studies could be included in the meta-analysis

However the definitions of care outcomes used in the testing and treatment of hepatitis C infection are relatively uniform in the literature, meaning that included studies adopted similar reporting points for data. The relevant outcome points: a diagnosis of hepatitis c; the concept of viral load, the process of linkage to care and uptake of drug treatment; the attrition from treatment; and the achievement of a cure (sustained viral response at 12 weeks post treatment-SVR12) were reported in a consistent manner.

The meta-analysis did show a consistent direction of effect and the study identified that uptake of drug treatment from studies carried out in primary care settings was approximately twice that recorded for uptake of drug treatment in specialist care settings. The ability to aggregate studies and to use a random effects model to weight individual studies meant that a more conservative summary statistic was produced than by the fixed effects model (Higgins and Green, 2011). The strength of evidence assessment used, also highlighted the areas where stronger and weaker support for the World Health Organisation guidance was available.

CHAPTER 4:

DEVELOPMENT AND MODELLING OF AN INTERVENTION IN COMMUNITY PHARMACY

Content

Radley A, Melville K, Easton P, Williams B, Dillon JF. "Standing Outside the Junkie Door" – Services users experiences of using community pharmacies to access treatment for opioid dependency. J. Public Health 2017; 39 (4): 846-855. doi:10.1093/pubmed/fdw138

Radley A, Melville K, Easton P, Williams B, Dillon JF (2017) was conceived by Radley and Williams. Radley and Melville undertook the qualitative interviews and jointly undertook the thematic analysis and interpretation. Radley, Easton, Williams and Dillon provided methodological and clinical advice. The paper and subsequent revisions were written by Radley and the final submission signed off by all co-authors.

Radley A, van de Pol M, Dillon JF. Designing a hepatitis C testing service in primary care: a discrete choice experiment. International Journal of Drug Policy 2019; 65:1-7. https://doi.org.10.1016/j,drugpo.2018.12.008

Radley A, van de Pol M, Dillon JF (2018) was conceived by Radley, van der Pol and Dillon. The questionnaire was designed by Radley and van der Pol using information from Radley et al (2017) as well as information gained from a literature review and published guidance on conducting discrete choice experiments. The analysis was led by van der Pol with input from Radley. The paper and subsequent revisions were written by Radley with input from van der Pol and Dillon and the final submission signed off by all co-authors

Radley AS, Melville K, Tait J, Stephens B, Evans JEE, Dillon JF. A quasi-experimental evaluation of dried blood spot testing through community pharmacies in the Tayside region of Scotland. Frontline Gastroenterology 2017; 8**:** 221-228. doi: 10.1136/flgastro-2016-100776

Radley AS, Melville K, Tait J, Stephens B, Evans JEE, Dillon JF (2017) was conceived by Radley, Evans and Dillon. The protocol and study documents were prepared by Radley and Dillon. Training and mentoring of the community pharmacists was undertaken by Radley and Stephens. Data acquisition was undertaken by Radley, Melville and Tait. Evans and Dillon provided methodological and clinical advice. The

analysis was undertaken by Radley with input from Evans and Dillon. The paper and subsequent revisions were written by Radley with input from Evans and Dillon. The final submission was signed off by all co-authors.

Evidence Contributions

These papers report on the development and modelling work undertaken to initiate and describe the pharmacist-led intervention, as part of the process of acquiring increasing evidence to inform the design of a definitive experimental study of a complex intervention using the Medical Research Council's Guidelines. The structure of the work enabled an iterative increase in understanding of how to construct an intervention that was feasible and pragmatic

The paper describing a focus group series (Radley et al 2016) illustrates the lived experience of people prescribed opioid substitution therapy and identifies a variety of themes that form a basis for a grounded approach to co-design of the intervention. The work enabled the priorities and perspectives of people receiving care through a pharmacy to be explored. Thematic analysis of the focus group content both confirmed issues discussed within the literature and contextualised the local delivery of care to this vulnerable group. Actor Network Theory was used for a theoretical perspective from which to understand the interaction of human and non-human actors in producing the outputs from care.

The paper describing a discrete choice experiment (Radley et al 2019) utilised themes identified from the focus group series plus several structural themes to design a questionnaire to evaluate the stated preferences of a cohort of people prescribed opioid substitution therapy. Analysis of the stated preferences demonstrated the clear importance of being treated with dignity and respect to the study participants. The importance of location, availability of test results, travel distance and incentives for participation in the service were also evaluated.

The paper describing a quasi-experimental approach to blood-borne virus testing in pharmacies (Radley et al 2017) demonstrates the implementation of the first part of the intervention and explores initial participant and provider views about delivery. Testing in a local pharmacy was demonstrated to be feasible, with uptake comparable to other providers. A process evaluation was undertaken and thematic analysis performed with the outputs available for comparison to the perspectives obtained in the focus group series and discrete choice experiment.

These papers are included here to record how the pilot and feasibility work have shaped and informed the subsequent development of the SuperDOT-C intervention. The lessons learned from this work were used to inform development of an experimental protocol to evaluate the pharmacy pathway.

Knowledge Translation Contributions

Radley has contributed to the development and implementation of a community pharmacy-based hepatitis-C testing service commissioned by the Welsh Government (WHC /2017/048 Eliminating hepatitis (B and C)) and to similar work undertaken by the London Clinical Commissioning Groups. The development work has been presented at local and international conferences as both poster and oral presentations and as a workshop format.

4.1 "Standing outside the Junkie Door" Service Users' Experiences of Using Community Pharmacies to Access Treatment for Opioid Dependency

The following paper is a verbatim copy of Radley AS, Melville K, Easton P, Williams B, Dillon JF. "Standing Outside the Junkie Door" – Services users experiences of using community pharmacies to access treatment for opioid dependency. J. Public Health 2017; 39 (4): 846-855. doi:10.1093/pubmed/fdw138

ABSTRACT

Aim:

To explore experiences of service users attending a community pharmacy to receive opioid substitution therapy (OST).

Method:

Qualitative study involving seven focus groups undertaken within care centres and prison educational centre in Tayside, Scotland using 41 participants. Thematic analysis undertaken of experiences of different groups of service users and carers.

Results

Participants described the social context surrounding attendance at community pharmacies. Their voices suggested that people prescribed OST may be treated differently from others accessing care through pharmacies. Participants felt they experienced stigma and discriminatory practices in pharmacies, elsewhere within the healthcare environment, and more generally in society. Participants explained that the way services were organised in pharmacies often denied them the right to confidentiality.

However, there were positive experiences of care. The discriminating factor between good and bad experiences was being treated with dignity and respect.

Conclusion

Participants readily identified examples of poor experiences and of stigma and discrimination, yet valued positive relationships with their pharmacy. Constructive attitudes of pharmacy staff and the ability to form positive relationships improved their experience. The social exclusion delivered through stigmatisation mitigates against delivery of a recovery agenda and contributes to health inequalities experienced by this marginalised group.

INTRODUCTION

Supervised consumption of Opioid Replacement Therapy (OST) has been the mainstay of treatment for people who use heroin for some time [1]. Drug users have attended pharmacies in Scotland to receive supervised administration of replacement drugs since the early 1990s. The shared care arrangement, between prescribers, specialist drug treatment services and community pharmacies reduces diversion of methadone into the illicit market and increases access to this treatment [2]. However, across Europe, treatment is mostly conducted in outpatient settings, which can include specialist centres, general practitioners and low-threshold facilities[3].

In practice, this means that service users attend a pharmacy on a daily or regular basis to receive doses of methadone or buprenorphine; this is intended to replace the consumption of heroin. The consumption of the OST dose may be supervised, or handed to the service user to consume off premises [2]. It is estimated there are 376,136 "problem drug users" in the United Kingdom, and 133,112 people who inject drugs (PWID) [3]. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) defines PWIDs as "ever injectors" among people tested in drug service settings [5]. In Scotland, approximately 59,000 people are identified as using drugs [6]. The number of opioid users prescribed treatment in 2011/12 was estimated at 149,000 in England and Wales [7]. An estimated figure Scotland would therefore be 22,224 [8].

There is strong evidence that OST improves a range of important outcomes [9]. Longitudinal studies identify that OST improves retention in treatment, reduces illicit use of substances and reduces levels of risk behaviours. Reduced criminal activity and improved health and well-being have been reported [10, 11, 12, 13, 14, 15]. There is also evidence of a positive correlation between "treatment dose" (numbers of attendances) and outcome [16]. The contribution of supervised consumption to recovery may be double-edged: creating a daily structure and reducing use of other opiates, but preventing engagement in recovery activities such as paid work. Supervised consumption is a central component of the United Kingdom policy framework [17]. Policy makers may view long-term maintenance on OST either as a positive step for harm-minimisation or as a barrier to achieving a drug-free lifestyle: moving OST users to a drug-free lifestyle remains a challenge[18].

The success of OST depends on engagement with services and adherence to therapy. The Drug Misuse and Dependence: UK Guidelines on Clinical Management [17] (also known as the Orange Guide) states that directly supervised OST by a professional for a period of

time provides the best guarantee that the medicine is being taken as prescribed. Supervised consumption as part of the recovery process may be protective and associated with a decrease in drug deaths and development of a therapeutic relationship. The journey of recovery may mean the movement to unsupervised consumption over time [19]. In practice, most OST is delivered by community pharmacists and increasing numbers of pharmacies provide needle exchange services [20]. Pharmacists and dispensing staff are central to the provision of OST [21]. Service users therefore may have more contact with the pharmacist than any other healthcare worker [22].

Despite growing evidence to support the delivery of therapeutic interventions through community pharmacies [23], there is evidence that outcomes obtained with OST can be improved [24]. A partial explanation for poorer outcomes may lie in service users' interactions within and around community pharmacy services [25, 26, 27, 28, 29]. Stigma, combined with a poor self image and apparent negative treatment may provoke negative behaviour and precipitate conflict [30]. Pharmacists may be reluctant to deal with a group of clients who may sometimes be abusive or intoxicated and may shoplift [2]

Although pharmacy service provision is extensive, there is little contemporary research describing the nature of these interactions with service users, associated problems, or likely solutions. This study was conducted to explore the current experiences of service users attending a community pharmacy and receiving OST in Tayside, Scotland.

METHOD

The study was conducted within care centres and a prison educational centre as part of a local Public Health needs assessment. A focus group methodology was chosen to enable participants to share experiences within a supportive environment. Utilisation of the group dynamic and involvement of participants in group discussions was employed to help manage impulsive behaviour and short attention span [31]. Effective management of these factors was believed to outweigh potential negative aspects of focus group approach including description of group normative experiences and the effect of inherent group hierarchies to suppress subordinate voices [32].

Study documents were submitted to the East of Scotland Research Ethics Service, who confirmed this work did not require Ethical Approval. Caldecott permission was gained to enable access to and analysis of patient information. A topic guide was developed from evidence syntheses and refined during the study (Appendix).

Sampling:

The study used a purposive sampling strategy to identify a diversity of likely views [33]. Individuals were eligible for inclusion if they received OST from a community pharmacy or were the carer of someone prescribed OST. We aimed to recruit around 40 participants. Recruitment focussed on the following variables:

-Place of Residence –large urban / other urban / accessible small town

-Service Users detained by the Criminal Justice System

-Perspectives of male and female service users

-Perspectives of peer mentors (service users at an advanced stage of recovery)

The sampling strategy was formulated to enable a diversity of views to be obtained, at different places within the network of actors and technologies [34]. Carers were included in the groups, since OST users experience long-term conditions at an earlier stage than the general population.

Recruitment & consent:

Potential contributors were identified through local support groups and care centres. Each person completed a consent form prior to participation. The patient information sheet was explained to each group by the facilitator to assist those with poor health literacy.

Data collection:

Seven focus groups with 41 participants (Table 1) were undertaken by AR and KM. Sessions were open-ended and ranged from 70–100 minutes. The first focus group served as an internal pilot to test the discussion guide. The seventh focus group with peer mentors, was undertaken to provide perspective on the findings from this study. In the local service configuration, peer mentors are experienced service users who have received OST for a number of years and are further along a recovery pathway: we listened to their reflections and perspectives on the themes that had emerged.

Table 1: Participant details

		Number of Participants
Age group at participation	Less than 35 years	17
	35 – 44 years	5
	45 – 54 years	6
	Over 55 years	4
	Did not disclose	9

Sex	Male	31
	Female	10
Participant category	Service User	38
	Carer	3
Number recruited defined by sampling frame	Large Urban Settlement	10
	Other Urban Settlement	10
	Accessible Rural Town	6
	Prison Educational Centre	7
	Women's Group	4
	Peer Mentor's Group	4

Analysis:

Data from each focus group were digitally recorded and transcribed verbatim. Both AR and KM undertook the coding and analysis (Box 1). Analysis drew on the constant comparison method, which was operationalised within a general thematic approach [35]. Analysis included five stages: familiarisation (reading and re-reading the transcripts), identifying a thematic framework (a key list of codes); applying the codes to the quotes in the transcripts; creating tables of quotes and comments to compare data across groups; mapping and integrating the key findings into a meaningful whole. Deviant cases were sought to identify opinions which modified or contradicted the analysis [36]

Box 1: Strategies Employed to Ensure Rigour and Trustworthiness
Deviant cases were sought to falsify theory
Iterative data collection utilise to ensure emergent themes could be explored
A checking strategy was used within interviews to check interpretation
Data analysis was conducted by more than one team member

In our analysis we drew on the work of Duff who utilises Actor Network Theory to portray the assemblage of spaces, bodies and effects, to characterise the context of drug use as the interrelation of people and technology [37, 38].

RESULTS

Service users were reflective about the circumstances that led to them receiving OST from a pharmacy. When asked about their experiences of attending a pharmacy, participants' responses were often passionately voiced. Focus group data demonstrated

interactions between different actors and technologies: with pharmacy staff; members of the public; pharmacy premises and adjacent environments; the rules used by the pharmacy to manage demands and workload.

Our analysis identified three key themes (Box 2). These are illustrated with quotes demonstrating typical or divergent responses. Quotes are labelled with participant number, sex and age.

Box 2- Themes Identified

Theme 1 – The social context surrounding OST users

Theme 2 – The interaction with pharmacy service delivery

Experience of stigma

Experience of discrimination

Issue of time

Issue of confidentiality

Positive Experiences of care

Service Users Explanations for their Experiences

Theme 3 – Making things better

The social context surrounding OST users

Service users provided vivid descriptions of life on methadone. Participants followed a daily routine of attending pharmacies, obtaining money, and avoiding trouble (Box 3, Participant 16). Some service users reflected on their preoccupation with obtaining drugs, legal and illicit. They felt that the centrality of OST in their life led to diminished horizons (Box 3, Participant 40). The day-to-day reality of OST use was one of continuous poverty: lack of money was a constant challenge; searching for enough money to pay for daily expenses; having bus money; the difficulties in maintaining employment (Box 3, Participant 20).

Box 3: The Social Context of OST

We are all shoplifters and we have all been stealing to feed wer drug habit. See when you first get out the jail you don't get paid for about a month, so, after 3 days you are skint. Until about a month later you need to walk all the way into the toon, sometimes its 4 or 5 miles just to get your Meth, and then you have to walk home another 4 or 5 mile back or you can go shoplifting to get money for the buses or

something. Ken what, its just how it is and that's how ye end up in the jail. Participant 20, Female 24 years.

It does occupy…it occupies most of yir day and night coz yir always thinking aboot whar yir gona get money. Participant 38, Male 37 years

I thought it was a life saver at the start ken I thought it was great when I got on it an got on it coz I thought it was another drug another charge and I wouldna wake up rattling. I thought I'd get my methadone then I'd go score drugs like 2 fixes, 2 hits sometimes 3 or 4.

That was my world, my hoose, the chemist and the boozer. Participant 40, Male 35 years

You are keeping yourself to yourself, you just got outa the jail and you are keeping your head down. You are not going out stealin but you are goin to that chemist. Y are taking that chance every day and you are seeing other drug users, right and it's li encouraging you. You are likely doing it, in a minute. First day out and you are pis off an somebody offers you something that will be it. Participant 16, Male 32 years

And if they know you then thats even worse. That's how I moved to somewhere I'm not from where I dinna know anybody and do you know what it's a hell of a lot bett It's so much better, I dinna get offered at the chemist cause no-one knows is. So ev though they see me going through that door because I dinna speak to anybody or giv away anything its brilliant honestly. I couldn't have made a better choice for me an my son to go somewhere where they dinna know my past, they dinna know who I ar they don't know what I've done do you know what I mean it's brilliant. Participant Female 28 years

A lot of people work that take methadone, a small majority, but they do and they wa normal life. That's how they are on methadone coz they want a normal life they widdnae be on methadone if they didnae want a normal life.

Participant 33, Male 38 years

The attraction of OST waned over time. Some participants explained how methadone and drug use became less important to them and family life and employment increased in importance (Box 3, Participant 33). Participants described how they changed their social networks to move away from drug use; they described the need for a 'normal life' (Box 3, Participant 18).

The interaction with pharmacy service delivery

Service users' often had both positive and negative experiences of community pharmacies. Participants provided accounts of positive relationships and contributions to care but many examples of poor experiences and unpleasant relationships were described.

Experience of stigma

Participants described real and current experiences of stigma. The idea that people would shun them was common. They felt set apart from other members of society (Box 4, Participant 18). Service users sensed this treatment was unjust; other people had chronic conditions such as heart disease and diabetes, which were also self-inflicted, but were not discriminated against (Box 4, Participant 22). People who abused prescription medication (benzodiazepines) were not treated as they were. Service users felt unfairly treated since they had chosen to change, through entering the OST programme.

Experience of discrimination

Participants felt that use of a range of different practices within pharmacies caused a distinction between people picking up a methadone prescription and people picking up other prescriptions (Box 4, Participant 8). Discrimination was conveyed in numerous ways, including restricted attendance times and additional bureaucracy (Box 4, Participant 20). In two focus groups, service users described how they were asked to leave young children outside the pharmacy. The women's group was particularly reflective on how they were treated differently and used the powerful metaphor of "Apartheid".

The use of a separate entrance or hatch automatically identified them as receiving methadone. Service users described using the hatch to receive their methadone and going to the "normal people's counter" to receive other medication. Even when a service user was prescribed unsupervised consumption of methadone, discriminative practices might prevent them taking their OST away from the pharmacy (Box 4, Participant 23). Service users were made to sign written agreements by the pharmacy. This was not done with other patient groups. Participants described using two pharmacies: one to receive OST and one to obtain their other medicines; to enable them to be treated as other patients were.

Box 4: The Organisation of Pharmacy Methadone Services

Experience of Stigma

And I was on the bus the other day and it was an old couple were like "yeah all they

junkies hanging about the chemist and it's the ones who've got kids going in to that bit that I feel sorry for" now they obviously didn't know that they were talking to like a methadone user. I felt like shit to be honest with you. Participant 18, Female 28 years

Yeah because I mean you wouldnae treat somebody different if they were a, a diabetic and they were standing in front of you eating a sweetie, ken I mean you wouldnae say tae them you shouldnae be dain that (mumbles). What's the difference between an addict and somebody that's say self inflicted a lot of heart disease is self inflicted, there's loads of things that are self inflicted so why dae they single out addicts or alcoholics. Participant 22, Male 37 years

The Issue of Discrimination

"If there is any more than two in the shop, if there are any more than two drug addicts in the shop, you have got to stand outside until one comes out. You are not allowed any more than two people in the pharmacy at the same time. It doesn't matter if its rain, sleet or snow, you stand outside. She frankly told us that she doesn't want us in there when there's people in there"

Participant 8, Male 32 years

what I mean because it is embarrassing ken you're standing there buzzing this buzzer and you've got to wait until they decide to pick up that phone and let you in so then there could be loads of people walking past you and you're standing there ken they could clearly a' ken that you're going awa' in there for that. Know what I mean. Participant 20, Female 24 years

First day she got methadone from the chemist she went tae take it oot the shop she went "thank you". "Oh hang on you need tae take that" she says "ah no I'm unsupervised" and the guy says "Oh no he says I don't do that, as far as I'm concerned I don't want methadone in the streets" Participant 23, Female 27 years

The Issue of Time

It's only half an 'oor, well the chemist I'm it you've got to go in efter half 9 in the morning right, you can go in at any time during the day. But it's other chemists, you go in, you've got to be in the 2 'oors and if you're no there for 5 o'clock well in the efternane if you're no there til 5 past 4 and you're meant to be there by 4 you dinna get yir methadone. That's wrang.

Participant 40, Male 35 years

and some days I'd wait, wait, waiting, wait some mare. I'd be waiting 15 minutes, 20 minutes, 25 minutes in some cases until one day I got pig sick fed up o it coz I would see folk walking in from the doctors surgery and walking out before them walking in after them. I counted half a dozen folk one morning that walked in after the three o them and walked out before them with prescriptions in their hand. Participant 34, Male 43 years

The Issue of Confidentiality

A couple of members of staff I would say are good but the rest of them nah, they look doon at you. I'd come off my methadone and went into rehab in November there and came off it and then I went into the chemist, but into the actual normal bit of the chemist and there was a prescription coming up from the DPC for a sleeping tablet 'cause I wasn't sleeping and when I went in the chemist was busy and the lady came over and she was like "could I help you" and I said yeah has a prescription come up from the DPC and she was like "what, for methadone?" right in front of everybody in that chemist. And I looked at her, and they all knew what I'd just been through, and I'm looking, going, for methadone I dinnae think so, ken what I mean, and I was absolutely, I'd just couldnae believe that she'd done that. Participant 18, Female 28 years

Positive Experiences of care

I got bloods ta'en and they think I've got pregnancy diabetes so I went in and was telling the woman that just through conversation and she said maybe it was just something that I ate that day and I said nah a' I had was, I had my methadone then I went right to the doctors to get the blood ta'en and she went well that could be what it was 'cause methadone's got that much sugar.

Participant 20, Female 24 years

Whan eh got stabbed Al did gie me a lot of coz they didnae stitch it, they left it open and it wiz quiet a big wide wound, mind that ain in my groin and it was mair A than the nurses coz eh wiz seeing her every day coz eh was only seeing meh doctors once a week and she wiz gieing me mair advice on how to keep it clean masel, dressings and this that and the next thing. So it was good.

Participant 26, Male 32 years

Service Users Explanations for their Experiences

You've got a lot of drug addicts that are gonna go about with baggage and go "oh I'm

an ex drug addict everybody's looking down their nose at me". They're gonna go about with that attitude and nine times out of ten they're actually attracting that from people they may not have got it from coz they learn to protect themselves. But nine oot of ten because o the way they have been treated they go in wi that attitude because that's the way that they have been treated"

Participant 21, .Male 41 years

The issue of time

The issue of time was consistently raised; the time wasted in pharmacies waiting to receive methadone (Box 4, Participant 34). The use of restricted attendance times was felt to be a unfair (Box 4, Participant 40). To complain about these arrangements risked getting put off the pharmacy list. This practice had real consequences and was used several times to explain why participants could not maintain employment. The attendance pattern meant that employers could guess that their employee was on methadone. The queue for methadone meant being brought into close proximity with undesirable people; drug dealers, people who might steal or create unpleasant situations.

The issue of confidentiality

Service users did not feel that their confidentiality was respected. Confidentiality in the pharmacy was undermined systematically: by the material and physical arrangements, by the procedures utilised to manage patients and through the actions and attitudes of staff members. These arrangements were described by participants using words such as "the junkie door" and "segregation". Service users described how queuing to receive their methadone identified their reason for attendance to any onlooker. Participants related how staff members spoke about their consumption of methadone within hearing of other patients (Box 4, Participant 18).

Positive experiences of care

Participants readily described care which made a significant contribution to their well-being. An important and recurrent finding from this work was the value of being treated with dignity and respect. Although focus group discussions always began with descriptions of poor experiences and difficult relationships, service users consistently spoke highly of "their pharmacist" and how the pharmacy they currently attended treated them well.

There was good awareness of the nationally organised Minor Ailments Service [39], through which they could access a range of medication for free. A variety of clinical interactions were described, from support with gestational diabetes to management of a traumatic

wound (Box 4, Participant 20, Participant 26). Where care was highly regarded, it was because positive relationships with staff were formed and maintained.

Service users' explanations for their experiences

Participants could understand the way that people treated them like this. The reasons arose from their own behaviours (for example shop-lifting), but also through the way they were forced to act through circumstances (experiences of stigma and discrimination) and the lifestyle they had adopted. There was a perception of shared responsibility for their treatment, with an acknowledgement that some service users expected poor treatment and acted accordingly (Box 4 Participant 21). The idea that a public face was assumed by the service user in order to protect their feelings was described several times.

Making things better

Participants expressed a desire to use the same consultation room as other pharmacy users, so that their care could be undertaken in private. It was acknowledged that the numbers of service users using pharmacies made this unlikely. Participants recognised the poor behaviours of a few individuals but there was general resentment that this led to all service users being treated in the same way. Focus group participants wished for the pharmacy service to operate more flexibly and responsively to their needs and support their process of recovery more actively. Participants described the wish to be treated as individuals rather than as a group (Box 5).

Box 5: Making things better

As I say I have no complaints about the pharmacy that I use. They're very good, there's a little consulting room you can sit. They take you into the consulting room you take your methadone and you leave, it's all done in private. If the consulting room's busy they use a wee space they've got through the back but they always ask you very nicely if you don't mind going through there. So, they're great. Participant 23, Female 27 years

You don't need anything else if you have got respect. If you get handed your methadone with a smile and asked how you are doing today. Participant 9, Male 38 years

In the first instance its likely you would still need to go every day but then again I mean the medicine is there to support your recovery and so it is about how you move forward and it should be fitting into your life as well. I mean the guys spoke earlier about they think it's better that you need to go in every day because

they remember the 80's when the streets were awash with methadone and stuff like that but it is a medicine like any other medicine and you know as you recover and as you change you become much more confident then the medicine should, it shouldn't hamper your recovery. Participant 32, Male 42 years

DISCUSSION

Main findings of this study

Participants in this research describe the social context surrounding attendance at community pharmacies: how the assemblage of networks of actors interplays with pharmacy services. Accounts demonstrate that people prescribed OST are managed differently from other patients. Service users experience stigma and discrimination in pharmacies, other healthcare settings and generally in society. The organisation of care in pharmacies effectively denies service users confidentiality.

Narratives about negative experiences were tempered by accounts of positive experiences of care. The discriminating factor between positive and negative experiences was that the service user was treated with dignity and respect. Service users easily identify poor experiences but also valued positive relationships with their current pharmacy.

What is already known on this topic?

Perspectives on treatment recovery have been described by other researchers [20, 31, 40, 41, 42, 43]. Evidence that service users are treated as an anti-social group has been reported [44] as has the detrimental consequences of pharmacy service organisation [26].

Participants described a common experience of discrimination and stigmatisation when accessing routine healthcare [45, 46, 47]. The parameters of stigma are well described [48]. The attitudes displayed by healthcare staff may mirror stigmatising attitudes across society [49]. However, stigmatisation mitigates against recovery and continues the health inequalities experienced by this deprived and marginalised group [50, 51, 52].

Most pharmacies in Scotland provide substance misuse services and many have created a separate facility for OST supervision [53, 54]. This practice may enhance a stigmatised identity, especially when coupled with explicit discrimination and prejudicial attitudes of staff [22, 28]. The use of waiting time to convey discrimination and create dependence is important [26, 27]. The restrictions on access and consequences on employability are described in several places [45, 55]. Employment is a key step in addressing health inequalities and social inclusion [56].

That drug misusers often steal and how this affects their treatment has been reported [55]. A study of attitudes of community pharmacists reported that about ten percent of pharmacists had negative views [53]. Work a decade later reported improved attitudes and increased service provision [21, 57]

What this study adds

This most striking finding of this study is that despite 25 years of service provision, problems with OST provision remain [53, 57]. Pharmacists may still be ill-prepared to manage difficult situations, when drug using clients behave aggressively or abusively, shoplift or are intoxicated [2]. The stigmatising attitudes experienced by service users are closely linked to policies on prohibition and criminalisation [49]

Limitations of this study

This study draws on the qualitative insights of service users experiencing care within community pharmacies. Use of a focus group methodology was clearly a viable method within the resource constraints of a public health needs assessment; however an ethnographic approach would contribute an alternative route to defining the effects of person place and time [58].

The authors reflected that the strength of some contributions could have been influenced by the group dynamic; descriptions of poor experiences may have been better accepted [31, 32]. The use of a female group was therefore undertaken, since male contributions were observed to dominate. We purposively recruited a group of experienced service users acting as peer mentors, to a final focus group and used this narrative to gain reaction to the findings and comment on themes [59].

CONCLUSIONS

Stigma, combined with a poor self image and apparent negative treatment may provoke negative behaviour and precipitate conflict [30]. Pharmacists may be reluctant to deal with a group of clients who may sometimes be abusive or intoxicated and may shoplift [2].

The social exclusion delivered through stigmatisation, mitigates against delivery of a recovery agenda for this multiply deprived and marginalised group [17].

Capitalising on the contribution that community pharmacy can make requires further work to improve the quality of relationships with service users. Service users have expressed the desire for more knowledgeable staff, capable of responding effectively to the issues that they bring [28]. It is likely that education and training as well as role support is required as well as steps to change organisational cultures within pharmacies in particular and healthcare in general [60]. This change however is within the current policy

intention for modernising the delivery of pharmaceutical care from community pharmacy [61]. Further research is therefore required to confirm that a positive change in practice is achieved. The references for this paper are provided in the manuscript located at Appendix 9.2

Appendix: Experiences and Views of People Using Pharmacies to Obtain a Methadone Prescription

i. Tea, coffee provided to participants as they arrived. This allowed individuals to talk to each other and establish introductions

ii. Participants were asked to introduce themselves and to say how they would like to be referred to.

iii. The purpose and confidentiality of the research was explained and clarified, along with general guidance to ensure a good quality recording was made (i.e. not talking at the same time as others).

iv. The following questions were used to guide the discussion, with sensitivity to the issues that were important to participants and also to the opportunity of each participant to contribute the issues and observations that were important to them.

Questions	Justification
Can you tell me about your experiences of obtaining your methadone prescription from a pharmacy? How would you describe your relationship with the pharmacist? Do you feel you are treated with dignity and respect at all by your community pharmacy? What positive features of getting treatment at a pharmacy would you like to see more of? What negative features of getting treatment at a pharmacy would you like to see less of?	General views on treatment of substance misusers in pharmacies Specific experiences of substance misusers in pharmacies
Are you aware of having a care plan in place with regards to your methadone treatment? Has anyone discussed the content/its meaning? Have you received a copy of your care plan? Would you like to receive a copy of your care plan? Do you think such a care plan would improve your relationship with the	Making sense of the interaction with the pharmacist Establishing aspirations for the content of the service

pharmacist? What types of issues would be important to be discussed as part of the care plan?	

v. Group Finish: Participants were asked if there were further issues and observations that they had not been able to contribute. The facilitator gave a summary of the key points covered from field notes and asked participants of the summary covered the issues as they saw them.

4.2 Designing a hepatitis C testing service in primary care: a discrete choice experiment

The following paper is a verbatim copy of Radley A, van de Pol M, Dillon JF. Designing a hepatitis C testing service in primary care: a discrete choice experiment. International Journal of Drug Policy 2019; 65:1-7. https://doi.org.10.1016/j,drugpo.2018.12.008

ABSTRACT

Background

Ascertaining the acceptability of healthcare provision to service users is an important factor in promoting service uptake, especially for populations who are reluctant to access care. This study identified the attributes of a Hepatitis C (HCV) testing service for people prescribed Opioid Substitution Therapy (OST) and used their expressed preferences to guide design of a service, using an applied health economics approach.

Materials and Methods

Preferences of OST users were elicited using a discrete choice experiment. Important attributes for HCV testing were partly pre-determined by the research question and also identified using literature review and focus groups. Predetermined attributes included choice of provider and financial incentives. Other important attributes were place of testing; travel distance; attitudes and staff undertaking testing; waiting time for test results and incentive payment. The relative importance of defined attributes was assessed in 103 OST users attending 6 pharmacies from Dundee.

Results

OST users preferred testing at their "own pharmacy", by their drug worker, followed by their general practitioner (GP). Use of another pharmacy was the least preferred option. Being treated with dignity and respect was valued most highly, with waiting time for test results and travel distance also important. Financial incentives were not considered important.

Conclusions

This study provides evidence that OST users prefer testing at their own pharmacy. The addition of a pharmacy to the providers offering HCV testing may increase uptake and support policies to eliminate HCV from our communities. Being treated with dignity and respect was highly valued and this suggests that testing uptake can be increased by developing positive relationships between OST users and test providers. Financial incentives were not found to be important.

INTRODUCTION

The World Health Organisation Guidelines on Testing for Hepatitis B and C establish critical enablers for the provision of efficient and effective services. Suggested best practice includes implementation of simplified, decentralised care pathways, with task-shifting to non-specialised staff (WHO 2017). Additionally such services should be delivered in a way that is acceptable to service users, especially for populations who are reluctant to access care. It is important also to consider testing as part of the continuum of care to HCV cure rather than an isolated step (WHO 2017).

In developed countries, people who inject drugs (PWIDs) are the major group affected by hepatitis C (HCV) infection (WHO 2016a). In communities where heroin is the principle drug injected research suggests that around 40% of people prescribed Opioid Substitution Therapy (OST) are infected (Aspinall, Doyle, Corson, Hellard, Hunt, Goldberg...Hutchinson 2015; Edlin, Kresina, Raymond, Carden, Gourevitch, Cheever, Cargill 2005). In current HCV testing and treatment pathways within the United Kingdom, less than 10% of the OST population are tested for HCV and a similar pattern is seen across the world: a depressing repetition of waterfall plots shows people with HCV infection are lost to care at each step (Iveson, Grebely, Catlett, Cunnigham, Dore, Maher 2017).

The barriers that prevent uptake of HCV testing and treatment have been characterised as system-level, practitioner-level and patient level (Grebely, Oser, Taylor, Dore 2013). At the system level services may still be based on a configuration designed to identify people suitable for interferon based treatment, with conventional pathways containing multiple steps (Arora, Thornton, Murata, Deming, Kalishman, Dion… Qualls 2011). These pathways may be further complicated by required actions by specific practitioners allowing access to services or remuneration for those services. At the practitioner level these restrictions also apply. Prejudice against PWIDs also operates with many practitioners having the expectation that people will not adhere to medical treatment. Health practitioners may not perceive HCV treatment as a legitimate activity within their practice and may not have the necessary skills and knowledge to be confident in discussing HCV treatment with the client group (Treolar, Newland, Rance and Hopwood 2010). At the patient level, people taking methadone may live in poverty and experience stigmatising and discriminating behaviour (O'Gorman, Driscoll, Moore, Roantree 2016). The need to travel to attend clinics decreases the numbers of people being tested (Astell-Burt, Flowerdew, Boyle, Dillon 2011; Monnet, Ramee, Minello, Joost, Carel, Di Martino

2008; Papatheodoridis, Tsochatzis, Hardtke, Wedeyer 2014) and proximity to services may be more important in rural communities. People who inject drugs may have shifting priorities between HCV treatment and other activities, may not have the relevant information about the treatment efficacy and side-effects of Direct Acting Antiviral (DAA) Medicines, may not seek out testing and treatment and may experience anxiety and confusion when offered opportunistic testing (Jones, Atkinson, Bates, McCoy, Porcellato, Beynon...Bellis 2014). Low levels of health literacy may limit understanding of their health, illness and treatments (Kalichman, Benotsch, Suarez, Catz, Miller, Rompa 2000).

Delivery of HCV testing and treatment through community-based care pathways has been shown to be feasible (Wade, Veronese, Hellard, Doyle 2016) and dried blood spot testing (DBST) has been demonstrated to increase the uptake of testing from high-risk populations (Coats & Dillon 2015; Taheri 2010; McAllister, Innes, Mcleod, Dillon, Hayes, Fox 2014). Testing in community environments in risk groups, can result in high levels of linkage to care (Tait, Stephens, McIntyre, Evans, Dillon 2013). The use of DBST in non-traditional environments has dramatically increased detection of HCV (Morana, Zelenev, Lombard, Marcus, Gibson, Altice 2014).

With appropriate training HCV testing can be carried out by a range of personnel, including community pharmacists (The Hepatitis C Trust 2018). Pharmacy provision has particular potential for the OST population as they have daily interactions with pharmacies. However, little is known about whether OST users would find testing at pharmacies acceptable and what other aspects of testing are important to them. To optimise uptake, it is crucial that HCV testing is designed in line with users' preferences (WHO 2016c).

In this study, a Discrete Choice Experiment (DCE) was used to elicit the preferences of service users who access OST from pharmacies, to help co-produce the design of an HCV testing service. DCEs are a commonly used stated preference technique for eliciting patient preferences for healthcare services in order to understand what attributes of a service are important and the relative importance of these attributes (Kjaer 2005).

The design of a service often requires trade-offs between attributes that are important to patients. For example, HCV testing can be provided at a pharmacy but the waiting time to test results may be longer compared to HCV testing by GPs. DCEs can elicit and quantify how patients make trade-offs between these attributes. DCEs are rooted in Lancaster's theory which relates the utility or value of goods and services to the

characteristics or attributes of the goods or services. DCEs present individuals with a series of hypothetical choices between different service configurations which vary in a number of characteristics or attributes (for example location of testing, waiting time etc). DCEs are also based on random utility theory (RUT) which means that the choice behaviour of individuals is assumed to be probabilistic rather than deterministic. This means that the utility (or value) of the healthcare service has a systematic component (such as the attributes) that can explain the choices individuals make within the DCE and a random component which include unobserved factors that can explain choices such as psychological factors.

A DCE approach has recently been used to elicit service user preferences for HCV treatment efficacy, the occurrence of adverse treatment effects and the degree of treatment burden (Mühlbacher, Bridges, Bethge and Nubling 2017). However no work has been identified that considers service users' preferences in terms of HCV testing and how they may trade off the different attributes of the testing, such as provider (location), travel distance and waiting time for results. The use of DCEs to predict uptake of treatment for new pathways of care is also a useful feature of this technique when addressing the need to deliver on the ambition to eliminate hepatitis C as a public health concern (Quaife, Terris-Presholt, Di Tanna, Vickerman 2018)

MATERIALS AND METHODS

The aim of this discrete choice experiment was to elicit OST user's preferences for HCV testing, in order to aid the design of a testing service that was acceptable to use from their perspective. The attributes and levels in the DCE were selected following recommended practice (Reed Johnson, Lancsar, Marshall, Kilambi, Mühlbacher, Regier...Bridges 2013). A number of attributes were predetermined by the research question. The aim of the DCE was to examine whether OST users may prefer HCV testing in pharmacy over other settings and provider of testing was therefore a pre-determined attribute. We were also interested in assessing the potential of using financial incentives, therefore financial incentive was also a pre-determined attribute (WHO 2016). A review of existing literature was undertaken to identify other attributes of HCV testing that are important to individuals. The themes identified through this process included medical and community clinic provision; travel distance from the clinic; the requirement for attendance at a remote site; the experience of stigmatising behaviour; the use of point of care testing and difficulties with taking venous samples (Wade, Veronese, Hellard, Doyle 2016; Harris

and Rhodes 2013; Arain and Robaeys 2014; Jones, Atkinson, Bates, McCoy, Porcellato, Beynon...Bellis 2014).

Focus Group Series

In order to test the relevance of these possible attributes to the target group and to explore whether there were any other important attributes, a focus group series was undertaken with service users to establish their views of current services and especially of their experiences of using community pharmacies to access care (Radley, Melville, Easton, Williams and Dillon 2016). Seven focus groups with a total of 41 participants (Table 1) were undertaken during 2015, in a range of settings, aiming to gain a diversity of views and experiences, until no new data (saturation) were achieved. Participants were people prescribed OST by the specialist substance misuse service in Tayside, who provide the majority of care for this group. Participants discussed comparative experiences of partners, family and associates who had undertaken testing and treatment for HCV.

Table 1 – Focus group participant profile

		Number of Participants
Age group at participation	Less than 35 years	17
	35 – 44 years	5
	45 – 54 years	6
	Over 55 years	4
	Did not disclose	9
Sex	Male	31
	Female	10
Participant category	Service User	38
	Carer	3
Focus Group Venue	Large Urban Settlement	10
	Other Urban Settlement	10
	Accessible Rural Town	6
	Prison Educational Centre	7
	Women's Group	4
	Peer Mentor's Group	4

Recruitment to the focus groups concentrated on the following variables:

-Place of Residence –large urban / other urban / accessible small town

-Service Users detained by the Criminal Justice System

-Perspectives of male and female service users
-Perspectives of peer mentors (service users at an advanced stage of recovery)
Sessions were open-ended and ranged from 70–100 minutes. The first focus group served as an internal pilot to test the discussion guide. The seventh focus group with peer mentors was undertaken to provide perspective on the findings from this study. In the local service configuration, peer mentors are experienced service users who have received OST for a number of years and are further along a recovery pathway: we listened to their reflections and perspectives on the themes that had emerged.
Data from each focus group were digitally recorded and transcribed verbatim, before being coded and analysed by two researchers. Analysis drew on the constant comparison method, which was operationalised within a general thematic approach (Richie and Spencer 1994).
Focus group participants described a range of attributes that had significant overlap with those identified from the literature: stigma, waiting times, confidentiality of results and positive relationships with service providers.
The final attribute list included the pre-determined attributes (who does the testing (provider) and incentive payment) as well as the most important other attributes identified through the literature review and focus groups (whether treated with dignity and respect; travel distance; and waiting time to test results). The larger the number of attributes, the greater the cognitively complexity of the DCE and therefore the total number of attributes was kept to a manageable level. Plausible levels were assigned to each attribute based on focus group responses and the local context for factors such as laboratory turnaround and travel distance. Table 2 presents the attributes and their levels.
Table 2 Definition of attributes and Levels

Time	Distance	Money received	Provider	Dignity/Respect
1 week	0.5 miles	0	GP	Yes
2 weeks	1 miles	£2	Drug Worker	No
3 weeks	2 miles	£6	Usual Pharmacy	
4 weeks	4 miles	£12	Other Pharmacy	

Figure 1 shows an example of a discrete choice scenario considered by participants.

Figure 1 Example of choice set

	Test A	Test B	
Where?	Your Usual Pharmacy	Your GP	
Treated with Dignity & Respect?	YES	NO	
Travel Distance?	Half a Mile	2 miles	
Time to get Results?	Two weeks	One Week	
£ You Receive?	£2	£4	
Which Test Would You Take? (√ only one)	Test A ☐	Test B ☐	No Test ☐

Given the number of attributes and their levels, the total number of possible combinations is equal to 512. This was reduced to 16 choice sets using a D-efficient main effects design with flat priors created in SAS (Statistical Analysis Software) (Burges, L and Street D 2005). An opt-out was included in each choice set. The design is presented in Appendix 1.

Design of the Questionnaire

The final study questionnaire contained three sections: Section 1 ascertained participants' preferences on the levels within the 5 attributes; Section 2 presented the 16 discrete choices; Section 3 collected details of patient demography including age, sex, educational level and employment. The cognitive burden of the choice sets in the questionnaire was of especial concern, because of awareness of potential issues with comprehension, literacy levels and attention spans in the respondent group (Borisova and Goodman 2004). Think aloud interviews were undertaken with 7 individuals to test the wording and check the understanding of the questionnaire design. Respondents completed the questionnaire in the presence of one of the researchers who provided support where required (Kronenberg, Slager-Visscher, Goossens, van den Brink, van Achterberg 2014). The

administration of the questionnaire in a familiar environment was also chosen, to reduce participant stress and enable access.

A total of 103 participants within six pharmacies in Dundee City that they used to access OST completed the questionnaire. All participants completed a consent form before completing the questionnaire.

Estimation procedure

In each choice set an individual was presented with a choice between three options (j): test A, test B or no test. It assumed that individuals will choose the option that they value most highly, that is, the option they receive the highest utility from.

The utility that an individual (*i*) receives from an option (V_{ij}) is a function of the attributes and levels included in the DCE:

$$V_{ij} = (\beta_0 + \sigma_0)Test_{ij} + (\beta_1 + \sigma_1)Other\ pharmacy_{ij} + (\beta_2 + \sigma_2)GP_{ij} + (\beta_3 + \sigma_3)DrugWorker_{ij} + (\beta_4 + \sigma_4)Respect_{ij} + (\beta_5 + \sigma_5)Travel_{ij} + \beta_6 Time_{ij} + (\beta_7 + \sigma_7)Money_{ij} + \varepsilon_{ij}$$

"*Test*" is the alternative specific constant which takes on the value of 1 if the option is either Test A or Test B and 0 if the option is No test. "*Other pharmacy*", "*GP*" and "*Drug worker*" are the provider, "*Respect"* is whether treated with dignity and respect, "*Travel*" is the travel distance in miles, "*Time*" is the waiting time for results in weeks and "*Money*" is the amount of money they receive if they take the test in pounds and ε_{ij} is the random error term. β and σ are the parameters to be estimated. The βs represent the average marginal utility of changes in the attribute. These can be interpreted as follows. For the quantitative attributes, a one unit increase (for example, a 1 week increase in waiting time) reduces utility by the size of the β. The qualitative attributes (provider and respect) are modelled using dummy coding. In this case the coefficients represent the difference in utility between the attribute level (for example drug worker) and the base category (for example own pharmacy). The σs represent the individual specific preference variation for the attributes. A statistically significant σ indicates that individuals vary in terms of how they value the attribute. The distribution of the coefficients was assumed to be normal. A fixed parameter was assumed for waiting time to stabilise the estimation process and allow for easier estimation of the willingness to wait (see below). This means that respondents were assumed to have the same negative preference for waiting time. The model was estimated using mixed logit regression in Stata using maximum simulated likelihood with 3000 Halton draws.

The relative importance of the attributes was assessed by estimating willingness to wait, calculated by dividing the estimated coefficient values of the attributes with the coefficient value of the waiting time attribute. This indicates how much longer individuals are willing to wait for a unit change in an attribute. For example, ($\beta_4/-\beta_6$) indicates how much longer individuals are willing to wait for their test results if they are treated with dignity and respect.

RESULTS

The sample characteristics of the respondents completing the discrete choice questionnaire are shown in Table 3. The sample closely mirrors the characteristics found in OST population in Dundee for the parameters of age (median age range 30-40 years), educational level (completed secondary school) and employment (registered unemployed or unable to work due to disability). The sample however contains approximately fifty per cent female respondents, whereas females represent around a third of the base population.

Table 3: Sample characteristics for discrete choice experiment questionnaire

	N	%
Gender		
Male	52	50.5
Female	51	49.5
Age		
Age 20-30	11	10.7
Age 30-40	54	52.4
Age 40-50	32	31.1
Age >50	6	5.8
Education		
Secondary school	65	63.1
Other professional or technical qualification after leaving school	32	31.1
University degree	5	4.9
Missing	1	0.9
Employment status		
Employed	12	11.7
Unemployed and seeking work	44	42.7
Unable to work due to illness or disability	45	43.7
Retired	1	1.0
Missing	1	1.0

Test A was chosen in 39.5% of choice sets, Test B in 48.8% of choice sets and in 11.6% of choice sets the respondents chose no test. Analyses of the "No Test" option identified that 68% of respondents did not choose this option for any of the discrete choice sets. Three percent of the respondents selected "No Test" for between 13 and 16 of the discrete choice sets.

Table 4 shows the regression results. The results show that individuals prefer to be tested at their own pharmacy. The coefficient on drug worker is not statistically significant indicating that own pharmacy and drug worker are equally preferred. Other pharmacy is the least preferred option.

Table 4: Regression results for the discrete choice experiment

	Coefficient (β)	p-value	Standard deviation of the random parameters (σ)	p-value	Difference in utility between best and worst level	Relative size of utility difference
Test	4.1687	<0.001	4.0466	<0.001		
Test location					0.959	21.7%
Other pharmacy	-0.9240	<0.001	1.1801	<0.001		
GP	-0.5518	0.002	0.9328	<0.001		
Drug worker	0.0348	0.835	0.7130	<0.001		
Treated with dignity and respect	2.1515	<0.001	1.9891	<0.001	2.152	48.7%
Travel distance (miles)	-0.2345	<0.001			0.704	15.9%
Waiting time for results (weeks)	-0.1138	0.003			0.398	9.0%
Money received (£)	0.0174	0.104			0.209	4.7%
N	4932					
Pseudo R^2	0.2739					
AIC	2005.354					

Being treated with dignity and respect, waiting time for test results and travel distance are all important to individuals. The sign of the coefficients is as expected with OST respondents preferring to be treated with dignity and respect, shorter travel distance and shorter waiting times for tests results. Money received is not significant suggesting that the use of financial incentives may not increase uptake of testing. There was statistically significant preference variation for provider (other pharmacy, GP and drug worker) and being treated with dignity and respect. There was no significant preference variation for travel distance or money received. Further analysis (including latent class modelling) suggested that preference heterogeneity was not associated with any of the observed individual characteristics

Table 5 provides further insights into the relative importance of the attributes by estimating the willingness to wait. Being treated with dignity and respect is of particular importance to individuals. They are willing to wait an additional 9.2 weeks for their test result if they are treated with dignity and respect. They are willing to wait an additional 3.9 weeks for their test result if the test is taken at their own pharmacy instead of another pharmacy and 2.4 weeks if the test if taken at their own pharmacy instead of their GP.

Table 5: Willingness to wait analysis

Willingness To Wait	Additional weeks willing to wait for test result	
	Mean	95% confidence interval*
Having test at own rather than other pharmacy	3.9	1.8 - 6.1
Having test at own pharmacy rather than GP	2.4	0.7 - 4.0
Having test at own pharmacy rather than drug worker	0.1	-1.3 - 1.6
Being treated with dignity and respect	9.2	4.9 - 13.5
Reduce travel distance by 1 mile	0.5	0.1 - 0.8
Receive an additional £1 for taking test	0.1	0.0 - 0.2

* estimated using the delta method

DISCUSSION

This study has examined OST users' preferences for hepatitis C testing using a discrete choice experiment, as a method to increase the acceptability of healthcare provision to

service users (WHO 2017). It provides supporting evidence of the importance of considering a range of factors when working to improve treatment access (Harris and Rhodes 2013). The results indicate that individuals prefer to be tested at their own pharmacy or by their drug worker. These two options are preferred to testing by GP or other pharmacy. Being treated with dignity and respect was the most important attribute with waiting time for test results and travel distance also being important to individuals. Being treated with dignity and respect was found to be the most important attribute for test decision making.

In this study, money received did not have a significant effect, suggesting that the use of financial incentives may not increase uptake of testing. However, it may be the case that respondents in our DCE ignored the incentives attribute because payments to produce changes in health behaviour remain controversial; individuals feel shame in accepting money for treatment of their stigmatised condition. Monetary incentives have been found to be helpful in promoting testing for HIV (Rakotonarivo, Schaafsma, Hockley 2016); a recent study has found that financial incentives could be applied to support treatment adherence in HCV care (Wohl, Allmon, Evon, Hurt, Reifeis, Thirumurthy...Mollan 2017). A small pilot study of incentives to promote HCV testing in a prisoner and parole population found little discernible effect from offering incentives (Grebely, Oser, Taylor and Dore 2013). This is in line with our DCE results but further evidence on the effectiveness of incentives in HCV testing is clearly required.

This study adopted accepted best practice in the use of qualitative methods to inform attribute selection (Zaller, Patry, Bazerman, Noska, Kuo, Kurth, Beckwith 2016; Kjaer 2005). The use of focus groups provided the researchers with a range of perspectives on the experiences of methadone users when using pharmacies as a service. The focus group series identified time as one of the important attributes. The value of time has previously been assessed in patients prescribed OST (Clark, Determann, Petrou, Moro, Bekker-Grob 2014) and is thought to be a good method of measuring relative importance. We used willingness to wait for test results as a 'currency' for expressing the relative importance of the different attributes of HCV testing. Willingness to wait has also been used with this patient group to evaluate treatment attendance (Borisova and Goodman 2003). Respondents in the focus group series reacted strongly to the issue of stigma and discrimination. This finding was also identified in the subsequent discrete choice experiment, where a service in which respondents were treated with respect was valued

highly. This suggests that getting providers to develop more positive relationships with OST users may be the most effective way to increase uptake of HCV testing.

A number of limitations are noted for this study. Firstly, the DCE choices were hypothetical. Individuals' real choices (the choices they would make in real life) may not always be the same as the choices they make in a hypothetical DCE. This is referred to as hypothetical bias and is a general limitation of DCEs. However, a recent review suggests that DCEs can make reasonable predictions of health related behaviour (Quaife, Terris-Presholt, Di Tanna, Vickerman 2018). Secondly, the lived experience of stigma was predominant in the focus group discussions and also the most important attribute within the DCE. The strength of this response meant that being treated with dignity and respect was the first concern of participants and may have been a dominant attribute within the DCE. As a result the other attributes may have had little or no impact on decision-making. As it is not possible to robustly assess whether any of the attributes are dominant within a DCE (Lanscar and Louviere 2006), this should be explored further using qualitative research. The cognitive burden of the choice sets questionnaire was carefully assessed by the authors, who were cognisant of potential issues with literacy, comprehension and attention span (Kronenberg, Slager-Visscher, Goossens, van den Brink, van Achterberg 2014). The method requires that the participant makes a series of decisions between a series of sixteen alternatives, in order to estimate which attributes are most important in decision-making. Strategies such as administration of the questionnaire by one of the authors, was used to ensure that respondents were able to provide accurate responses. Female participants were relatively over-represented amongst those choosing to take part in the DCE. The choice-set questionnaires were administered in the consulting rooms of pharmacies, where the female participants could obtain privacy to express their views. DCEs ask respondents to make hypothetical choices. Disparities between revealed and stated preferences have been termed hypothetical bias. Hypothetical bias may originate from a number of sources, including where choice tasks do not fully reflect reality, where respondents have incomplete preferences or if respondents perceive a vested interest in over- or under- reporting the importance of particular attributes (Quaife, Terris-Presholt, Di Tanna, Vickerman 2018). Such an effect may be important for respondents where the lived experience of stigma is such an important factor in decision making.

CONCLUSION

Provision of simplified, decentralised care for treatment of HCV is one of the key enablers for achieving the WHO target for HCV elimination (WHO 2016). The use of

task sharing with non-HCV specialists is also important to increase the service capacity available for care provision. This study demonstrates the acceptability for provision of testing in community pharmacies and evidence that the addition of a pharmacy to the range of providers offering testing can make a contribution to the elimination of Hepatitis C from our communities. Being treated with dignity and respect was clearly the most important attribute of a testing service and this study provides evidence that uptake of HCV testing can be increased by developing more positive relationships between OST users and providers.

The references for this paper are provided in the manuscript located in Appendix 9.3

Appendix 1. DCE design

Option	Choice	Provider	Respect	Distance	Wait	Money
Test A	1	Drug worker	No	4	4	2
Test B	1	Other pharmacy	Yes	2	2	6
Test A	2	GP	No	1	2	0
Test B	2	Own pharmacy	Yes	2	3	12
Test A	3	Other pharmacy	No	2	1	2
Test B	3	Drug worker	Yes	1	2	6
Test A	4	Other pharmacy	Yes	0.5	2	2
Test B	4	Drug worker	No	2	4	0
Test A	5	Other pharmacy	Yes	1	4	0
Test B	5	GP	No	4	1	6
Test A	6	GP	Yes	4	3	0
Test B	6	Drug worker	No	1	1	2
Test A	7	Other pharmacy	Yes	4	3	6
Test B	7	GP	No	2	2	12
Test A	8	Drug worker	Yes	2	3	0
Test B	8	Own pharmacy	No	4	4	12
Test A	9	Other	No	4	2	0

		pharmacy				
Test B	9	GP	Yes	0.5	4	6
Test A	10	GP	No	0.5	3	12
Test B	10	Own pharmacy	Yes	4	2	2
Test A	11	Other pharmacy	Yes	1	1	12
Test B	11	Own pharmacy	No	2	2	6
Test A	12	GP	No	1	1	6
Test B	12	Drug worker	Yes	0.5	2	12
Test A	13	Drug worker	No	0.5	3	2
Test B	13	Own pharmacy	Yes	1	4	12
Test A	14	GP	Yes	1	3	2
Test B	14	Other pharmacy	No	0.5	4	6
Test A	15	Own pharmacy	No	1	3	2
Test B	15	Drug worker	Yes	4	1	12
Test A	16	GP	Yes	2	4	2
Test B	16	Own pharmacy	No	1	3	12

4.3 A quasi-experimental evaluation of dried blood spot testing through community pharmacies in the Tayside region of Scotland

The following paper is a verbatim copy of Radley AS, Melville K, Tait J, Stephens B, Evans JEE, Dillon JF. A quasi-experimental evaluation of dried blood spot testing through community pharmacies in the Tayside region of Scotland. Frontline Gastroenterology 2017; 8**:** 221-228. doi: 10.1136/flgastro-2016-100776

ABSTRACT:

Objective: Comparison of uptake of dried blood spot testing (DBST) for Hepatitis C infection (HCV) between community pharmacies and established services.

Design: Quantitative evaluation of a service development with qualitative process evaluation undertaken in parallel.

Setting: Six pharmacies from 36 community pharmacies within Dundee City, a large urban settlement with high levels of socioeconomic deprivation.

Participants: Patients in receipt of Opioid Substition Therapy (OST) not tested for Hepatitis C within 12 months. The 6 pharmacies provided OST for approximately 363 patients from a cohort of 1,385 patients within Dundee City.

Intervention: Provision of DBST by pharmacists.

Main Outcome Measure: Receipt of DBST between January and December 2014

Results: 43 of 143 service users with no record of testing from the 6 community pharmacies accepted a DBST. Of 561 from remaining 1022 service users with no record of testing, 75 were tested for HCV (30% Vs 13%). The OR for increased uptake of testing within the 6 pharmacies was 2.25 (95% CI 1.48 to 3.41, Z statistic = 3.81 p= <0.0001) compared to other services. The DBST taken by the pharmacies provided 12 patients with a reactive test. The process evaluation identified key themes important to staff and recipients of the service. A logic model was constructed.

Limitations: Non-experimental service evaluation performed in community pharmacies records service activity in one location across single time period.

Interpretation: Some evidence that DBST from community pharmacies may be feasible. Service users received the service positively. Staff reported that DBST was straightforward and achievable.

BACKGROUND

Hepatitis C (HCV) is a blood-borne viral infection causing liver disease. Around 1% of the population may be infected with HCV and around 0.8% are chronically infected [1]. The greatest risk of acquiring the virus in the UK is through injecting drug use. Patient outcomes from HCV infection vary, with 25% clearing the infection spontaneously and the remainder becoming chronically infected, risking development of cirrhosis and hepatocellular carcinoma. People infected with HCV may show no symptoms, presenting with incurable, end-stage disease. A recent Public Health England report highlighted that less than 3% of those known to be infected with HCV are being treated and less than half of those infected are known[2]. The largest single infected group are those on opiate substitution therapy (OST) [3]. Research suggests around 40% of people receiving OST have HCV [4, 5].

The conventional NHS pathway of care is that patients with a history of intravenous drug use or those currently prescribed OST should be offered HCV testing [1]. Testing is commonly available from a range of primary care and third sector providers. Once diagnosed, patients may be referred to nurse led treatment pathways, based around hepatology or infectious disease teams in secondary care.

In current pathways, less than 10% of the OST population are tested for HCV. Of those tested, at very best 25% start treatment in one of the dedicated centres, with 70-80% successfully completing. This means that only 2-3% of this vulnerable population receive adequate treatment [2]. The new highly effective Directly Acting Antiviral (DAA) drugs achieve cure rates in excess of 90%, with once or twice daily tablets for 8-12 weeks and few side-effects [6].

The use of Dried Blood Spot Testing (DBST) in non-traditional environments has dramatically increased detection of HCV [7, 8]. DBST has been shown to be a reliable alternative to taking venous blood samples and determining HCV status in drug injectors. With appropriate training it can be carried out by all staff. Several practice-based projects have sought to implement DBST into pharmacy practice [9].

Pharmacists have daily interactions with patients receiving methadone and we hypothesised that this relationship could be wielded to deliver increases in rates of testing using a DBST approach. To test this we employed a quasi-experimental design [10] to compare the uptake of DBST for HCV in a small group of community pharmacies, with uptake in established services (those in substance misuse services, general practices and in third sector organisations).

METHODS

A quasi-experimental design was chosen as a pragmatic route to evaluate the feasibility and scalability of a service development in community pharmacy, because of uncertainties about the effect size and nature of the intervention [11].

This study was carried out in the city of Dundee, within the Tayside region of Scotland, a large urban settlement with significant socio-economic deprivation [12]. There are 36 community pharmacies that provide OST for approximately 1,385 patients, within a total population of 148,000 [13]. Six pharmacies were trained to offer DBST. Pharmacies were selected if they provided OST supervision for at least 30 patients and staff were willing to participate. Patients in the comparator group were prescribed OST and attended a community pharmacy that did not offer DBST.

Design of the Intervention

Focus group interviews

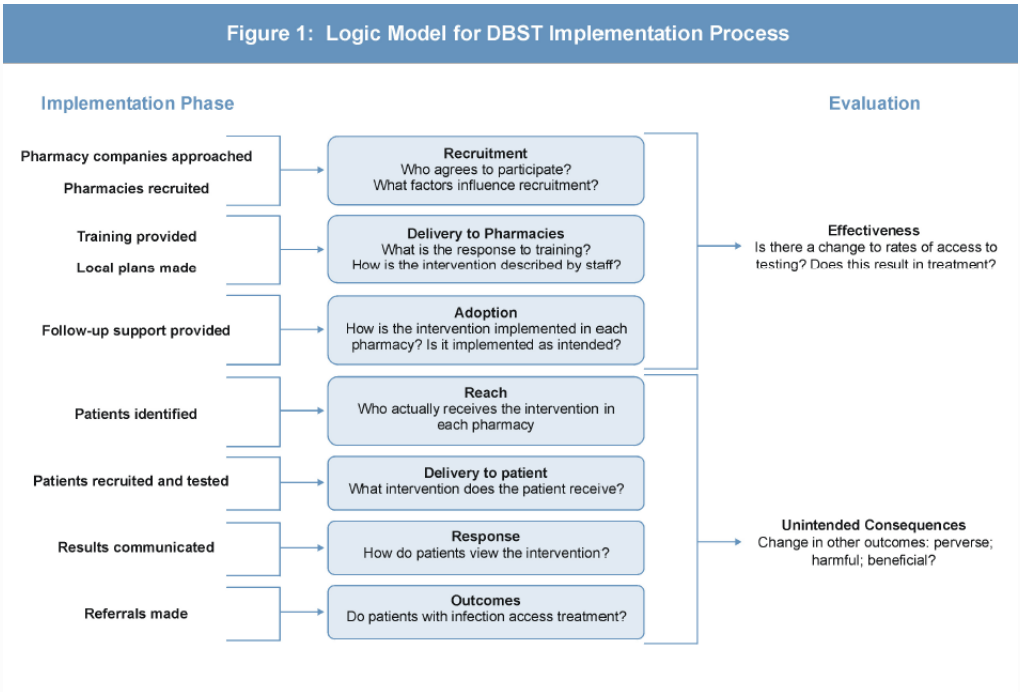
A focus group series was undertaken before implementation to identify service user responses to the offer of testing, utilising a co-production approach [14]. A purposive sampling strategy recruited 41 participants in 7 focus groups, to gain a diversity of views (Table 1). All interviews and focus group discussions were recorded as digital audio files and transcribed in full for thematic analysis [15]. Analysis drew on the constant comparison method, operationalised within a general thematic approach [16].

Table 1: Focus Group Participant details

		Number of Participants
Age group at participation	Less than 35 years	17
	35 – 44 years	5
	45 – 54 years	6
	Over 55 years	4
	Did not disclose	9
Sex	Male	31
	Female	10
Participant category	Service User	38
	Carer	3
Focus Group Venue	Large Urban Settlement	10
	Other Urban Settlement	10
	Accessible Rural Town	6
	Prison Educational Centre	7
	Women's Group	4
	Peer Mentor's Group	4

Development of Programme Theory

Figure 1 describes a logic model that was constructed to explicitly identify targets for evaluation and data collection. The process evaluation took cognisance of Normalisation Process Theory [17] using the core constructs of coherence, cognitive participation, collective action and reflexive monitoring to conceptualise the processes involved with effectiveness of implementation.



Implementation of DBST

Staff from the six community pharmacies were trained to perform DBST to consenting patients[18]. DBST employs a finger prick of blood, spotted onto protein saving paper. The sample was tested by Medical Microbiology for HCV, HIV and Hepatitis B antibodies [7]. Fourteen staff members from the pharmacies attended a 2 hour interactive teaching session. The six pharmacies were notified which of their OST patients had no history of HCV testing, as identified by the central virology laboratory. Testing for HCV was offered to each of these individuals. All individuals with a reactive antibody HCV test were offered referral to the specialist hepatitis service.

Participants' comments during the training were noted and each pharmacy was visited several times to discuss progress. Notes of these interactions and e-mails from participants were retained for analysis. Testing took place during the last quarter of 2014.

Post-Testing Interviews

Semi-structured interviews were conducted with (i) 8 service users and (ii) 10 professionals taking part in the study, with all 6 pharmacies represented. The interviews were conducted using two topic guides developed in line with the research aims and programme theory. All interviews were recorded as digital audio files and transcribed in full for thematic analysis[15, 19]. These data contributed to assessment of feasibility and acceptability (including barriers and facilitators); identifying any unintended consequences of participation. Transcripts were inductively analysed to identify themes

emergent from the interviews. A deductive analysis was also undertaken to compare findings with programme theory.

Quantitative Data collection and analysis

Data on demographic information, risk factors, laboratory tests, referral, follow-up and treatment were collected. The age structures of the intervention and comparator groups were compared by t-test, as were data on DBST taken by the pharmacies. An odds ratio was calculated for the numbers of service users undertaking testing at pharmacies compared to non-pharmacy services.

RESULTS

The age structure of the 143 service users (26% of all OST users) with no record of testing from the 6 pharmacies, together with the 1022 service users of the comparator group are presented in Table 2.

Table 2: Age structure of service users prescribed OST in Dundee

Age	Intervention Cohort	Intervention Cohort (%)	Comparison Cohort	Comparison Cohort (%)	Total Population	Total Population (%)
<19	0	~	0	~	0	~
20-24	14	4%	23	2%	37	3%
25-29	51	14%	133	13%	184	13%
30-34	112	31%	256	25%	368	27%
35-39	86	24%	239	23%	325	23%
40-44	61	17%	185	18%	246	18%
45-49	26	7%	120	12%	146	11%
50-54	10	3%	48	5%	58	4%
55-	3	1%	16	2%	19	1%

59						
60-64	0	0%	2	0%	2	0%
65-69	0	0%	1	0%	1	0%
	363	100%	1023	100%	1386	100%

Analysis of the age structure of intervention and comparator groups was undertaken. A significant difference between the two groups was detected using the two-sided t-test ($p<0.05$). The intervention group were younger by 1.75 years (mean age of 35.6 years) compared to the comparison group (mean age of 37.4 years). The study design meant that intervention and comparison groups were not randomised, and therefore equal mean ages of the two groups were not expected.

During the test period, 43 (30%) of the 143 service users from the six community pharmacies accepted a DBST. Within the comparator group 561 from 1022 service users had no history of DBST and a total of 75 (13%) patients were tested for HCV by other providers of DBST (30% Vs 13%). The OR for increased uptake of testing within the six pharmacies was 2.25 (95% CI 1.48 to 3.41, Z statistic = 3.81 p= <0.0001) in comparison to the other services (Table 2). The six pharmacies identified 12 patients with a reactive test. The uptake of DBST by each of the six pharmacies is presented in Table 3. No significant difference in uptake between the sites could be detected at the $p<0.05$ level using two-sided t-testing.

Table 3: Uptake of testing by pharmacy site

Pharmacy Site	Number of Eligible Patients	Number of tests taken (% of eligible patients)	Number of Positive Tests
A	23	13 (57)	3
B	22	11 (50)	4
C	30	5 (17)	3
D	26	10 (38)	1
E	26	3 (12)	1
F	16	1 (6)	0
Totals	143	43 (30)	12

Understanding of context for delivery

Themes identified from transcript analysis of the focus groups provided information about the context for delivery[20]. Focus groups discussions demonstrated an understanding of HCV including latency and effects on general health (Figure 2). Participants could talk about cirrhosis and cancer. Participants knew about the burden of treatment of interferon-based regimes. Several clients knew about the cost of the new treatments.

Hepatitis C was viewed as a "dirty disease" caught from sharing needles. It was unacceptable to admit to having HCV and participants feared social exclusion if found out. Participants described the shame they expected to feel if their family discovered they had HCV and spoke about "letting them down". The fear of being found out contributed to reticence about testing.

What factors influenced client recruitment and participation?

The transcripts from the post-test interviews demonstrated that service users had both positive and negative perceptions of testing. Interviewees clearly thought that pharmacies were a good place to be tested and valued this service and the positive relationships built with pharmacy staff. Lack of money meant travelling to a local hospital was a barrier to clinic attendance. Service users talked vividly about their diminished horizons: they felt this was due to their dependence on drugs and lack of money. Pharmacies however were viewed as part of the local community.

Some service users' previous experiences of stigma and discrimination when attending a pharmacy led to caution and suspicion when they were offered testing. One client complained that they were offered DBST stood at the dispensary counter, rather than in the private consultation room. Clients with negative experiences suggested staff would need intensive training before offering the service. Some clients expressed the wish for a better explanation about how the test worked and what the results might mean. Clients with positive experiences raised no issues for service improvement.

Several interviewees distinguished themselves from other "junkies". These interviewees would describe their plans for recovery and would describe their relationship with a partner or young family. These individuals believed that service users with more chaotic lives were less likely to be tested.

What feedback on staff training and implementation was received?

Staff interviewees had clear views about successful implementation. Staff considered that strong leadership and involving all the team were necessary. Comments such as “a great opportunity”, “an obvious thing to do” and “a no brainer” were made. The degree of enthusiasm for new roles and positive relationships with patients were important. Only one individual viewed the development “as a step beyond what pharmacies do”. There were some initial anxieties expressed about potential contact with infected blood. Some staff viewed DBST as a pharmacist’s role, whereas others thought it was a team role. The training was evaluated positively, with comments received about the simplicity of DBST. Several teams took lancets and protein-saving cards with them to practice the technique. Implementation was viewed as most successful where all the team were involved.

Some staff expressed concern about offering DBST when prescription dispensing workload was high. An identified solution was to use time slots when workload was less. Time barriers were most important where DBST was seen as a pharmacist role

Figure 2: Examples of focus group quotations

What do service users understand by hepatitis C infection and how they obtain testing and treatment?
Perceptions of disease "my daughter and partner have it. It can lie dormant. it makes you feel very tired and you have no appetite" (Participant 5, Carer, December 11) "You could have hepatitis even though, you could be stable on methadone for years then find out you've got hepatitis" (Participant 35, 22 April) Perceptions of testing and treatment I think more people have got it done since they started doing that 'cause it's easier (DBST) (Participant 37, 22 April) "What they do is they have a look at your white blood cells count and things like that and how your system is reacting to it and whether or not. See, when you get the finger prick test for Hepatitis it'll, if you have been exposed to the Hepatitis virus at all, it will come back positive. That doesn't necessarily mean to say that you have got Hepatitis, so what they then is they will do a blood test and start talking about counts and things like that as its really confusing" (Participant 19, 25 February) You see my partner is really skinny as it is and I think he will loose, everybody;s different are they, I think he will loose a lot of weight and I think it affects them mentally as well (Participant 33, 7 March) Preferences for obtaining treatment It would have tae be someplace where dinnae have tae travel everywhere where its gonnae cost them money that they have nae always got that's, that's what I feel is a big thing having tae travel tae Ninewells all the time (Participant 27, 5 March) I think that's one of the things that's gonnae be down tae the individual, it depends on how chaotic their lifestyle is otherwise there's gonnae be a lot of money wasted there. And I take it this new stuff isnae cheap coz it never is when its first introduced. (Participant 22, 5 March) "Well I say your pharmacy because like I say you're there every day, you're only, some people dinna even go to the DPC once a month. So and then you forget your appointment, some people forget their appointment at the DPC but you're guaranteed to go for your methadone every day so" (Participant 36, 22 April) Aye but you could be going tae the pharmacy for anything you see, so this again de-

stigmatising. Nobody knows what they're in there for, it could be a drug problem it could be… anything (Participant 19, 25 February)

DISCUSSION

Key findings

This study provides some evidence that pharmacies may be a feasible site from which to offer DBST. People receiving OST were more likely to accept a DBST from a pharmacy than from other local providers. The evaluation of the implementation provides some evidence of the context for delivery and the mechanisms that may lie behind the outcomes observed[20]. Contextual factors included: expectations and experiences of stigma and discrimination; fears about confidentiality; the limited horizons of people receiving OST and the poverty they experience. Identified mechanisms that may influence uptake included the presence of established relationships with pharmacy staff; a pre-existing reason for attending the pharmacy for OST and the proximity of the pharmacy within the local community.

Review of programme theory

The programme theory provided a useful structure from which to consider the process evaluation and enabled a series of insights into the barriers and facilitators to effective implementation. In particular, we valued insights into the context that testing in pharmacies created for service users and the meaning that such testing may have. The evaluation also provided an indication about how the attitudes and behaviours of staff towards the intervention contributed to success or otherwise.

A number of barriers to uptake of testing and treatment including fear of blood tests[21], adverse socioeconomic and family circumstances, as well as fear of treatment side-effects were identified in other studies as well as being identified in this study[22]. Evidence suggests that offering DBST may increase the uptake of HCV testing, when compared to venepuncture, although this finding may also reflect increased availability and access when a DBST technique is used [7, 23, 24]. Community-based settings for HCV services may also increase acceptance and uptake of testing [25, 26, 27, 28]. Provision of on-site testing may also have positive effects on uptake, due to the proximity of the testing offer[23].

Different settings have been used to increase the uptake of testing and treatment including testing from methadone maintenance services[29, 30,] in city homeless shelters[23] and mental health sites[26]. Little work has utilised the daily interaction with community pharmacists to increase testing, follow-up and treatment adherence. A pilot project introducing DBST

in a community pharmacy was undertaken in England in 2009[31, 32]. The pilot concluded that community pharmacies provide a useful route to diagnosing HCV patients and could successfully reach at-risk groups. The pilot service was most successful when pharmacists worked closely with local drug services and where pharmacists were proactive in discussing risks with clients. Several limitations were noted, including the availability of consultation rooms in pharmacies, the provision of adequate staffing to manage the normal workload of a pharmacy and also the motivation and commitment of the pharmacist to support this new activity. Similar factors were identified in this current study. The provision of clinical standard consultation rooms is now very common in Scotland.

The stigma associated with both OST prescription and HCV infection was strongly recognised in this study. A systematic review of qualitative research into Hepatitis testing, recommended framing the positive outcomes of testing in terms of responsibility for individual health and the health of family and community, building positive relationships and targeting stigmatising attitudes[23].

Limitations

The primary limitation of the current feasibility study is the small group of pilot pharmacies. Further work is now required to establish stronger evidence that pharmacies can positively influence uptake in a greater variety of locations.

The intervention group had a slightly lower average age than the comparator group. Since patients on OST undertake a pathway to recovery, a younger patient group may be expected to have a less stable situation than an older group and be less motivated to engage in healthcare interventions.

Some variance in service delivery is common place in pharmacies and in health services generally. The variance may be explained by a range of factors including staffing levels, building configuration, profile of the client group, as well as staff attitudes. With more experience of delivering training for and services, as well as role acceptance, it is expected that some of the variance will diminish.

INTERPRETATION

The study design provided a rapid and simple method of demonstrating that the systems required for DBST testing can be established successfully in community pharmacies. The daily attendance at the pharmacy provides an unexploited opportunity to deliver health interventions. OST recipients usually lived a short walk from their pharmacy

An increase proportion of OST service users accessed DBST from a pharmacy, compared to other providers. Knowledge of potential issues with implementation should assist with creation of effective service delivery. Further work to evaluate the outcomes associated with this service configuration is required[34]. The identified barriers to the uptake of testing in this study were overcome by local availability of the pharmacies and positive relationships with pharmacy staff.

The references to this paper are located in the manuscript provided in Appendix 9.4

4.4 Critical Reflection

This early phase of my research programme required a steep personal learning curve, both in terms of developing and documenting plans for research, but also in terms of becoming familiar with the procedures and implementation of research administration and governance.

Focus Group Study: The focus group study provided my first comprehensive conversations with the group of people who receive methadone prescriptions from pharmacies, even though these were through the medium of the focus group discussions we undertook. The focus group sessions were set up through third sector organisations and support groups, who both helped with the organisation and with the identification of participants. I was partnered at the focus groups by a colleague who led the substance misuse services and prescribed medicines for a caseload of clients that she looked after. Professor Williams provided guidance and support on method development and implementation.

The types of experience related within the focus groups were often very professionally challenging for me to listen to. These experiences provided me with a first real understanding of how stigma and discrimination are built in to systems and organisations. Prior to this work, I had no proper understanding of how stigma affected people using pharmacy services. An appreciation of how pharmacies operate services and how policies that were seemingly organised to ensure safety and efficiency, in fact cause discrimination and abuse was a key factor in the adoption of Actor Network Theory as a conceptual framework used to underpin the analysis of the transcripts. The focus group study provided a series of rich narratives to illustrate the motivation for this. For example, the pharmacy policy of only dispensing opioid substitution therapy (OST) for two hour periods in the morning and afternoon meant that the people receiving their supervised prescription, all had to arrive within a short space of time. This concentration of people who inject drugs (PWIDs) provided an attractive opportunity for drug dealers, who would loiter around the vicinity of the pharmacy. This phenomenon had a number of consequences for the behaviour of the recipients of the OST, who were brought into close contact with people they might like to avoid. The title of the paper “Standing outside the junkie door” is a quotation from one of the focus group sessions undertaken, and relates to the practice by pharmacies of enforcing separate entry arrangements for PWIDs and keeping them apart from “the normal people”. The separate entrance and the need to

queue outside and be admitted one-by-one meant that the individuals prescribed OST were denied confidentiality.

My professional manager also found the work challenging and objected to my plans for publication, because of the potential for damage to be done to professional relationships. To ensure that the pharmacy professionals had the opportunity to comment and provide "balance", I was required to present my results to a range of committees including the Area Pharmaceutical Committee, the Pharmacy Contractors Committee, Public Health Pharmacy Network, the Royal Pharmaceutical Society and the Chief Pharmacist at the Scottish Government. I completed the consultation and published the manuscript. Interestingly, not one of the bodies that I presented the results of the research to challenged my findings and I was able to undertake use the findings to provide awareness training for community pharmacy staff and present the findings about stigmas to a series of professional meetings.

Discrete choice Experiment: In order to better understand the theoretical basis of the method, I attended a four day course at the Health Economic Research Unit of Aberdeen University. This course covered the underpinning principles and used practical worked examples to apply this knowledge. The course was particularly useful in helping me to understand the way that the analysis is performed and some of the subtleties behind the calculations.

The findings from the focus group series were used directly to inform the selection of attributes for the discrete choice experiment. In preparing the manuscript for the focus group series, I undertook a rapid review of the literature surrounding provision of OST and identified key concepts that would make likely attributes for the research project. Many of the attributes identified from the literature search were confirmed through the focus group discussions. Themes such as stigma and discrimination, time, relative poverty and health literacy were easily identified as important factors that could be evaluated through this method.

I also undertook the task of piloting and administering the questionnaire and collating and presenting the results for analysis. The questionnaires were administered in the consulting rooms of pharmacies. The routine for this was to sit in the room and ask for the pharmacy staff to send through clients who might be interested in completing the survey, then providing them with an information leaflet and an explanation of what the study entailed. The following day, I sat in the consulting room of the pharmacy and waited for the clients to attend the pharmacy and then come and speak to me.

The positive relationships between the pharmacy staff and the clients of the pharmacies I had chosen meant that this was a relatively easy exercise (although with long periods of waiting). The interviews were undertaken in six pharmacies and just over one hundred participants were recruited from a potential population of about two hundred clients. The analyses of the questionnaires demonstrated how the client group lived around the pharmacy, did not usually complete school and were not employed. The people who chose to take the questionnaire were always friendly and willing to participate in something different and were very happy to explain why they selected the options they did. The clients that attended these pharmacies had good experiences of the pharmacies they had settled with.

One of the most memorable reactions of participants to the questionnaire was their reaction to the "treated with dignity and respect" option. Participants reacted very strongly to this option and often related previous poor experiences. The strong reaction to this option often dominated the participants' responses to the questionnaire, with the "treated with dignity and respect" option overshadowing other options. Discrete choice experiments, as a stated preference technique, are subject to hypothetical bias – where people say they would do something in theory, which they do not enact in practice. I reflect that the stated preference of the participants to be treated with dignity and respect was so strongly felt that it is likely that they would act on this.

Quasi-Experiment Evaluation: The implementation of this study required that I designed and delivered training to pharmacy staff from the study sites and created an operational route for pharmacies to submit blood tests that they had taken and receive results. The organisation of this made significant use of the relationships that I had established in Tayside and my knowledge of the people and services and how they worked. In particular, there was a need to negotiate with the Pharmacy Superintendent's Head Office to enable pharmacy multiples to participate in the study, which required tenacity and patience.

The design of the study was supported by Dr Evans who provided advice on use of the quasi-experiment method. Use of this approach enabled additional value to be gained from a small-scale pilot of part of the care pathway that had been designed and provided a platform for working through some of the factors that would be required to successfully deliver a full study.

The quasi-experimental evaluation of dried blood spot testing was undertaken in the same pharmacies as the discrete choice experiment. Pharmacy staff were trained during a

series of evenings in one of the pharmacies in Dundee that had a seminar room. Staff took readily to the dried blood spot testing procedure and enjoyed the chance to undertake something different. The relationships built during the previous work meant that the staff members understood what was required and were generally enthusiastic.

The pharmacies were successful in engaging their clients to undertake a test. This is a consequence of the positive relationship that the pharmacies had with their clients, but also may have been influenced by the conversations that had been undertaken during the discrete choice experiment. The interviews undertaken with clients as part of the study identified that the relationships with the pharmacy staff were valued, but also that the local situation of the pharmacy meant that the participants did not need money for bus fare and the competing priorities of the day, did not sidetrack them from taking a test. The pharmacy staff who were interviewed also responded positively to the opportunity to do something different and to take on a task that gave them some autonomy.

The use of a logic model and the adoption of a realist approach to the process evaluation were as a result of a series of study days provided at the University and consequent discussions with Professor Williams. The interviews were transcribed and then analysed using a Framework Approach, employing a simple spreadsheet to collect and organise the themes and quotations.

4.4.1 Critique of methods

Focus Group Study: The methods utilised for the focus group series are presented in chapter two and in the paper, therefore and a further in-depth discussion of the strengths and weakness of this approach will not be repeated. However, in summary, a focus group approach produces a normative dialogue of the issue under discussion, by the groups of participants. Care has to be taken to manage dominant voices and to gain a balanced account of the views of all participants. The facilitator of the focus group must be aware of reflexivity. Measures should be put in place to support vulnerable participants both during and after focus groups discourses, so that any distress that they experience may be managed (von Benzon and van Blerk L 1995).

One of the journal reviewers of the focus group manuscript suggested that a focus group methodology was not the best way to identify this type of data and that an ethnographic approach would be preferable to the approach I had selected. I defended my choice in the response to reviewers, from the perspective of being able to deliver a purposive sample from a range of locations of interest and being able to use the focus group discussion

dynamic to encourage the sharing of different experiences. The use of an ethnographic approach would require intense and long term investigation in order to collect data and record sequences of events: conversations between people and their relationships and therefore be used to document the experiences of the people using pharmacy services. Such as approach would be resource intensive and would deflect from my primary objective of designing and evaluating a care pathway to treat hepatitis C.

The themes emerging from the focus groups were very prominent and were easily identified by myself and my co-investigator with whom I undertook the focus groups and jointly undertook the thematic analysis and interpretation. The point where saturation of themes was reached and no new perspectives were being described probably occurred after the fourth focus group. The purposive sampling plan we had devised meant that we continued with the series and in particular, arranged a group with women's voices (since female focus group participants were less vocal than the males), and also undertook a peer mentor group. The motivation for this being that peer mentors would have a more longitudinal and reflective view of their experiences with methadone. The peer mentor session was also undertaken as a way of addressing the concerns of my professional manager: the views expressed by peer mentors were less likely to be from people with a particular grievance to air.

Discrete Choice Experiment Study: The methods used for this stated preference study are discussed in chapter two, with the strengths and weakness of the approach being set out also in the published paper. These will therefore not be repeated here. However generally, discrete choice experiments provide a means to systematically organise the preferences of a cohort of participants for the relative importance of a series of attributes that describe a product or service. Discrete choice experiments have a series of limitations that include the cognitive burden of the questionnaire and the number of choice sets presented, the potential for the hypothetical choices made by participants to difference from the choices they would make in the real world and the difficulty in selecting a representative sample of scenarios from the full range of possible combinations that are available (Reed Johnson, Lancsar et al 2013). In this study, the cognitive burden was managed through administration of the questionnaire rather than leaving the clients to complete it themselves. The language used in each of the scenarios was piloted with a "think aloud" group who were able to discuss how they understood each question.

Quasi-Experimental Evaluation: The approach used in a quasi-experimental evaluation together with the general advantages and disadvantages attributable to the method are discussed in chapter two and in the paper. These points will therefore not be repeated, but in general, a quasi-experimental evaluation provides weaker evidence of causality due to the non-random allocation of the comparator group. This leads to the possibility of systematic bias being present in the data that may affect analysis, meaning that researchers should be cautious in drawing inferences and conclusions since a range of alternative explanations for the data may be feasible.

The construction of a logic model to identify key stages of the intervention and critical points for data collection, proved to be a useful way of thinking through the processes involved in the study. Normalisation process theory was also invoked as a systematic tool for considering how the new processes involved in the intervention were incorporated into the work systems in each pharmacy (Murray, Treweek et al 2010). This proved to be most useful since the extent of testing each pharmacy actually achieved was very variable. A series of themes were identified which staff used to explain this finding. Where the whole pharmacy team took on the task, then the pharmacy was very successful and recruited a larger number of clients. Where the testing was made the responsibility of just one member of staff (perhaps the pharmacist), then fewer tests were performed. This result was thought to be about how well the team functioned and how effectively the pharmacist was able to display leadership of the team, which is coherent as assessment made using the theory.

4.4.2 Critique of analysis

Focus group study: The analysis of the study was achieved using a Framework approach in which two researchers familiarised themselves with the transcripts (reading and re-reading the transcripts), identifying a thematic framework (a key list of codes); applying the codes to the quotes in the transcripts; creating tables of quotes and comments to compare data across groups; mapping and integrating the key findings into a meaningful whole. The management of the data achieved using an Excel spreadsheet rather than NViVo (QSR International). For this study with a small number of transcripts to consider, this proved manageable and straightforward.

The identification of Actor Network Theory as a theoretical standpoint from which to undertake the analysis proved helpful (Latour 2005). Once the concept of non-human actors being able to influence behaviours and actions of human actors was understood, the

interactions seen became significantly clearer. In particular, the influence of organisational policies and the way these changed the way that clients in the pharmacy reacted to the pharmacy staff, other customers and each other was particularly helpful. A comparative theoretical approach that was also considered is the risk environment perspective (Harris and Rhodes 2013), in which a person's actions are held to be shaped by "critical transitions". The influence of non-human actors in the behaviours of clients visiting pharmacies to receive their methadone, was a key factor in choosing Actor Network theory.

The researchers were aware of the dominance of male voices in some of the groups and for this reason chose to organise a women's group to help acknowledge any possible imbalance in the data collected through a purposive sampling strategy. This proved to be worthwhile, in terms of the quality of some of the narrative that was gained, although the dominant themes were still present. Similar findings were identified in the peer mentor's group when this was analysed.

Discrete Choice Experiment: The analysis of the study was carried out using a standard approach using SAS (Statistical Analysis Software) (Burges, L and Street D 2005). Professor van der Pol provided the expertise and supervision for this analysis and also explored a conditional logit analysis and latent class modelling using Stata (Timberlake Consultants Ltd). However, the outcomes from these analyses showed that preferences did not systematically vary by the observed individual characteristics and so the simple analytical model was adopted for the paper.

The most prominent finding of the study was the importance of dignity and respect. The strength of this finding makes it likely that this attribute is indeed the dominant factor that guides whether a person takes up the offer of testing. The positive relationship developed between the client and the pharmacy, also has face validity since these relationships are likely to be maintained over a number of years once a client is settled at a pharmacy. It is however likely that the strength of response to the opportunity to be treated with dignity and respect, meant that the range of other attributes received less consideration from participants. The strength of reaction to the dignity and respect attribute also means that this finding is also less likely to be subject to hypothetical bias.

Quasi-Experimental Evaluation: In the analysis of this study, the data from all existing testing facilities were available as routinely collected data and it was a relatively simple exercise to gain the data for testing from these services and to use as the comparator. An analysis of the age profile of the pharmacy cohort showed significant differences in the

age profile when compared to the general population of tested participants: the pharmacy cohort were younger. This finding was rationalised within the study through the fact that younger participants would be at an earlier stage in their recovery journey and that these clients were likely to have a more chaotic lifestyle and therefore be less inclined to accept the offer of a test than older patients. However, the imbalance does show that some systematic differences were present in the study, as suggested by the discussion of the methodological approach in chapter two.

The process evaluation was a useful exercise to help establish explanations for the findings seen. The realist approach of "what works, for whom, in what circumstances" was an essential tool in helping to understand that the context for delivery of the intervention varied according to each location. The evaluation interviewed a series of clients who had undertook the test and staff who had provided the test. The semi-structured interview approach was helpful in enabling candid views to be expressed, out of hearing of other patients or a pharmacy manager. The opportunity to probe an expressed statement with a follow-up question also proved to be helpful in gaining an understanding of how the intervention had worked in practice

Overview of the development and modelling: The focus group, discrete choice experiment and quasi experimental evaluation studies provided the opportunity to gain significant insights into the parameters that might affect the operation of a pharmacist-led testing and treatment intervention. In particular, the findings around the importance of stigma and discrimination and also the manner in which clients formed positive relationships with a particular pharmacy were most informative.

Apparent weaknesses in particular methodological approaches were felt to be minimised by the ability to triangulate findings between different methods. The coherence of information generated by the programme and the building of expertise and knowledge about how the intervention was likely to operate, built confidence in the development of feasibility work to implement the full pathway.

CHAPTER 5:

FEASIBILITY ASSESSMENT AND EVALUATION OF A CARE PATHWAY FOR TESTING AND TREATMENT OF HEPATITIS C INFECTION IN COMMUNITY PHARMACIES.

Content:

Radley A, Tait J, Dillon JF. DOT-C: A Cluster Randomised Feasibility Trial Evaluating Directly Observed Anti-HCV Therapy in a population receiving opioid substitute therapy from community pharmacy. International Journal of Drug Policy 2017 DOI: 10.1016/j.drugpo.2017.05.042

Radley A, Tait J, Dillon JF (2017) was conceived by Radley and Dillon. Radley and Dillon undertook the protocol preparation. Radley prepared the ethics submission and designed study documentation. Radley undertook study staff training and acted as principal investigator. Radley and Dillon provided methodological, professional and clinical advice. Radley and Tait undertook the collection and preparation of the data. Radley undertook the analysis of the data. The paper and subsequent revisions were written by Radley and the final submission signed off by all co-authors.

Radley A, de Bruin M, Inglis S, Donnan PT, Dillon JF. Clinical effectiveness of pharmacy-led versus conventionally delivered antiviral treatment for Hepatitis C in patients receiving opioid substitution therapy: A study protocol for a pragmatic cluster randomised trial. BMJ 2019. DOI: 10.1136/bmjopen-2017-021443

Radley A, de Bruin M, Inglis S, Donnan PT, Dillon JF (2019) was conceived by Radley, de Bruin and Dillon. Radley prepared the ethics submission and designed study documentation. Radley undertook study staff training for all sites with Inglis and acted as principal investigator for Tayside sites. Inglis contributed to staff training and acted as trial manager. Radley, de Bruin, Donnan and Dillon provided methodological, statistical, professional and clinical advice. The paper and subsequent revisions were written by Radley and the final submission signed off by all co-authors.

Radley A, de Bruin M, Inglis S, Donnan PT, Hapca A, Barclay ST, Fraser A, Dillon JF. Clinical effectiveness of pharmacy-led versus conventionally delivered antiviral treatment for Hepatitis C in patients receiving opioid substitution therapy: a pragmatic cluster randomised trial. (Prepared for submission to The Lancet November 2019)

Radley A, de Bruin M, Inglis S, Donnan PT, Hapca A, Barclay ST, Fraser A, Dillon JF (2019) was conceived by Radley, de Bruin and Dillon. Radley prepared the ethics submission and designed study documentation. Radley undertook study staff training across the 5 research study sites and acted as principal investigator for the three Tayside study sites. Barclay acted as principal investigator for the Glasgow site and Fraser acted as Principal Investigator for the Grampian site. Radley, Barclay and Fraser contributed to local intervention implementation, practice and patient recruitment, study monitoring and data collection. Inglis contributed to staff training and acted as senior trial manager and performed the randomisation. Radley, de Bruin, Donnan, Barclay, Fraser and Dillon provided methodological, statistical, professional and clinical advice. Radley and Hapca devised the statistical monitoring plan and did the analysis. Radley and de Bruin designed and implemented the process evaluation. The first draft of the paper and subsequent revisions were written by Radley with contributions by all co-authors.

Evidence Contributions

These papers report on the feasibility trial and subsequent work undertaken to design a definitive experimental study of a complex intervention: a community pharmacy care pathway for testing and treatment of hepatitis C. This chapter therefore reports on the application of the learning gained from the development phase of the research programme.

The feasibility randomised controlled trial was undertaken to test the different elements of the pathway as a coherent whole. The study required that the pharmacy staff in the intervention arm recruited and tested patients, then diagnosed hepatitis C infection and assessed patients for treatment, before delivering treatment and confirming a cure. Interviews with pharmacists and study participants were undertaken in order to gain views and perspectives on the operation of the study pathway and of any insights into the operation of the delivery of the study that could optimise the effectiveness and efficiency of the definitive study.

The published study protocol describes the work that was undertaken to plan and prepare for the definitive trial of the pharmacist-led pathway. The paper sets out the experimental design and planned analysis and describes the administration of the study. The protocol also includes some commentary on how the preparatory work included in the research programme aimed to provide a pragmatic intervention and evaluation, capable of being delivered in practice.

The SuperDOT-C manuscript reports on the final stage on implementation of the research programme and the contribution to the evidence base on the ability of community pharmacy services to test and treat hepatitis C. The analysis demonstrates a strong indication that community pharmacists can increase the numbers of people with hepatitis C that access care and achieve a cure for the infection.

Knowledge Translation Contributions

This work has been presented to the Scottish Directors of Public Health and Scottish Government representatives, as well as to a United Kingdom-wide pharmacy conference. The clinical results have been reported at a conference at the Royal College of Physicians of Edinburgh. Study outcomes have been presented at local and international conferences as both poster and oral presentations and in workshop formats.

5.1 DOT-C: A Cluster Randomised Feasibility Trial Evaluating Directly Observed Anti-HCV Therapy in a population receiving opioid substitute therapy from community pharmacy

The following paper is a verbatim copy of Radley A, Tait J, Dillon JF. International Journal of Drug Policy 2017 DOI: 10.1016/j.drugpo.2017.05.042

ABSTRACT:

Background

Direct-acting antiviral therapy (DAAs) for hepatitis C infection (HCV) have a much smaller burden of treatment than interferon-based regimes, require less monitoring and are very effective. New pathways are required to increase access to treatment amongst people prescribed opioid substitution therapy (OST).

Method

An exploratory cluster randomised controlled trial with mixed methods evaluation was undertaken to compare the uptake of dried blood spot testing (DBST) and treatment of people with genotype 1 HCV infection in a conventional service pathway versus a pharmacist-led pathway in a population receiving OST.

Results

Pharmacies randomised to the conventional pathway obtained 58 DBST from 244 patients (24%):15 new reactive tests and 33 new negative tests were identified. Within the pharmacist-led pathway, 94 DBST were obtained from 262 patients (36%): 26 new reactive tests and 54 new negative tests were identified. Participants in the pharmacist-led pathway were more likely to take a DBST ($p<0.003$). Of participants referred for treatment through the conventional pathway, 4 patients from 15 with new reactive tests (27%) attended clinic for assessment. In the pharmacist-led treatment pathway, 20 patients from 26 with new reactive tests (77%) attended for assessment blood tests. Participants in the pharmacist-led pathway were more likely to proceed through the assessment for treatment ($p<0.002$). One participant completed treatment through the conventional pathway and three patients completed treatment through the pharmacist-led pathway. The process evaluation identified key themes important to service user completers and staff participants.

Conclusion

The study provides evidence that testing and treatment for HCV in a pharmacist led-pathway is a feasible treatment pathway for people who receive supervised OST

consumption through community pharmacies. This feasibility trial therefore provides sufficient confirmation to justify proceeding to a full trial

INTRODUCTION

Hepatitis C (HCV) is a blood-borne viral infection (BBV) causing liver disease. Around 0.8% of the Scottish population are chronically infected with HCV (Scottish Intercollegiate Guidelines Network, 2013). A recent Public Health England report highlighted that less than 3% of those known to be infected with HCV are being treated and less than half of those infected are known (Public Health England, 2018). The largest single infected group are those on opioid substitution therapy (OST) (Arain, 2014). Research suggests around 40% of people receiving OST have HCV infection (Aspinall, 2015; Edlin 2005).

The world-wide burden of HCV infection has been estimated as 71.1 million infections (62.5—79.4), with the largest group being genotype1 (Polaris Observatory HCV Collaborators 2017). The increased morbidity, mortality and economic impact of the infection are of concern to both industrialised and developing countries (Lavanchy, 2009).

The paradigm shift resulting from the introduction of Direct-Acting Antiviral therapy (DAAs) has changed the narrative around HCV, with a realisation that HCV could be eliminated in people who inject drugs (Lima, 2015). There is optimism that the use of DAAs offers a high chance of clearance of HCV infection from the population (Grebely, 2014). Treating all patient groups with HCV would yield substantial benefits (van Nuys, 2014) but there are concerns that the infrastructure and treatment capacity to deliver the required health outcomes are not generally available or of insufficient scale (Leask, 2016).

Treatment uptake for HCV amongst people who inject drugs is currently low (Weissing, 2014) and prospective patients may have a number of barriers to overcome in order to access care (Fernandez-Montero, 2014). There are identified deficiencies in the extent of screening and diagnosis of at-risk populations, as well as improvements required in access to treatment initiation and clinical monitoring (Artenie, 2015): People who inject drugs may find it difficult to consistently attend medical clinics (Papatheodoridis, 2014). However, the delivery of HCV testing and treatment through community-based care pathways has been shown to be feasible (Wade, 2016) and Dried Blood Spot Testing (DBST) has been demonstrated to increase the uptake of testing from high-risk populations (Coats and Dillon, 2015).

Creating the complex interventions necessary to eliminate HCV infection requires that well-designed cross-disciplinary programmes are put in place (Suther and Harries, 2015) using different strategies to increase screening, testing and diagnosis (Brouard et al, 2015). The potential of community pharmacy practices to make a greater contribution to the health of their local populations has been recognised for some time (Anderson et al, 2009). Pharmacists have long had a major role in delivering OST to this group of patients with a high prevalence of HCV (Anderson, 2007) and pharmacist involvement in delivering HCV treatment through multi-disciplinary clinics has been described for some time (Kolor 2005, Arora 2011)

The Tayside region of Scotland has sequentially developed integrated HCV treatment services over the last two decades, moving from standard secondary care-based hospital outpatients, onto nurse-supported treatment services, then to a HCV managed care network (MCN) including a widespread dry blood spot testing programme in drug services and development in our outreach services across the region. This most recent development includes providing treatment within drug services and prisons (Tait 2016). The network aims for wide involvement in BBV testing and follow-up, with healthcare professionals such as drug workers, GPs, prison nurses and social workers taking the opportunity to discuss referral and treatment with patients.

A cluster randomised feasibility trial was therefore designed to optimise the research design and consider whether a pharmacist-led testing and treatment pathway could be both effective and successful, before being more widely implemented (Bowen et al 2009). The study was designed with a mixed methods approach to evaluate: whether people who receive OST for pharmacies could be recruited to the study; whether pharmacies could successfully complete all elements of the testing and treatment pathway; which elements of the pathway work well and which elements are less successful; to make an estimate of the effect size in terms of how many participants complete each stage of the pathway (Eldridge et al 2016; Arain et al 2010).

In preparing to undertake this study, work was undertaken using a co-production approach in partnership with OST patients (Radley et al, 2016) and has developed the intervention through using the views of patients and staff to identify barriers and facilitators to effective care (Radley et al, 2017). The DOT-C study utilises the existing pharmacy environment and therapeutic relationships to smooth the pathway into HCV therapy and co-administer OST with anti-HCV therapy under the supervision of the pharmacist. The conventional care pathway requires referral and attendance of the patient

at another site and treatment according to the established standard of care. This feasibility study therefore aims to address questions about increasing testing and uptake of treatment, through a simplified community pharmacist-led care pathway for patients with genotype 1 HCV and to incorporate these colleagues into the work of the MCN.

METHODS

Trial design:

A cluster randomised feasibility trial of directly observed anti HCV therapy versus conventional care in HCV positive patients attending a pharmacist delivered OST program.

Study protocol: Ethics approval was received for this study (15/ES/0086) from East of Scotland REC2 on 2 July 2015. Caldicott Guardian approval was given on 25 July 2015

Participants:

Approximately 2,200 patients are prescribed OST within the Tayside region of North East Scotland. Around 85% of these patients receive daily supervision of their OST consumption through the 92 community pharmacies. At least 40% of these patients will be infected with HCV, 40% of infections are Genotype 1 virus (Hutchinson et al, 2006).

Trial inclusion criteria

Pharmacies were eligible to participate in the study if they could offer DBST for HCV or be trained to do so. Pharmacies required around 30 patients to ensure adequate recruitment.

Patients were eligible to be consented to the study if they were prescribed OST with supervised administration by a pharmacist and had a reactive DBST. Only genotype 1 patients were included. Genotype 3 patients were excluded because of the requirement to provide interferon-based regimes at the time of the study.

Randomisation:

Eight pharmacies were randomised into two groups: conventional care and pharmacist-led care. Randomisation was carried out using http://www.randomization.com. The subjects were randomized into one block using the seed 12576 along with the number of subjects per block/number of blocks and (case-sensitive) treatment labels. The pharmacy provided the level of randomisation, so patient allocation was dependent on the pharmacy attended.

Interventions:

All pharmacy staff involved with the study received training on good clinical practice, study procedures and documentation. Patients confirmed as having genotype 1 HCV

infection were assessed for suitability for treatment with ledipasvir 90mg/sofosbuvir 400mg (Harvoni®, Gilead) (EMC, 2016).

Conventional care pathway

In these pharmacies, the pharmacist opportunistically discussed with the patient the possibility of HCV infection and provided verbal and written information about testing and or treatment. If the patient consented and had not been recently tested, a DBST was taken and sent to the local laboratory. In Tayside, the DBST reports Anti-HCV, Hepatitis B surface antigen (HBsAg) and Anti-HIV. DBSTs reactive for anti-HCV are confirmed through venepuncture and PCR to determine genotype and viral load.

The local laboratory sent back the result of the DBST to the pharmacist, with results for HCV, hepatitis B and HIV (NHS Tayside MCN, 2012). The identity of each patient approached and the result of their DBST was recorded on a screening log. For patients with a reactive DBST, a standard referral letter was sent to the treatment centre and an appointment letter issued, inviting the patient to attend a clinic. For patients admitting to a recent HCV test, a standard referral letter was also sent to the treatment centre as described above. For patients attending the appointed clinic, assessment and treatment was carried out as normal within the standard of care.

Pharmacist-led pathway

In these pharmacies the pathway was identical to the conventional pathway, except that patients with a reactive DBST were assessed by the pharmacist for treatment. For consenting patients, the pharmacist completed a pre-treatment checklist of co-morbidities, medical history and concomitant medication. The patient was invited to attend a local phlebotomy service and have a panel of blood tests taken including markers of liver fibrosis (Castera, 2012) and viral parameters (genotype and load). The pharmacist used a Fib 4 test result to identify patients that required further assessment and input from the hospital-based multi-disciplinary team (Sterling 2006). Patients with a score of 3.25 or above were excluded from the study and referred to the multi-disciplinary team. These bloods were part of standard care for HCV treatment and are not research specific (i.e., they were also part of the conventional pathway). If the pharmacist identified no contra-indications to HCV therapy, the patient was commenced on treatment. Prescriptions were written by a pharmacist independent prescriber. In patients with potential contraindications or queries about suitability, the pharmacist contacted the central clinical co-ordinator for medical review. Unsuitable patients were referred for assessment outside the study, through the conventional care pathway. Patients received daily HCV treatment

at the same time as their OST, (usually on 5 or 6 days, so a modified version of DOT). For weekend doses (when the patient self-administered), the pharmacist and patient made a brief if-then action plan (an implementation intention) and coping plan (to overcome anticipated barriers) (Gollwitzer and Shearer, 2006).

Outcomes:

Participating pharmacies were asked to test all consenting and eligible patients from the cohort who attended the pharmacy. Trial outcomes were (1.) The proportion of OST patients accepting the offer of testing, (2.) the proportion of patients undertaking assessment for treatment, (3.) the proportion of patients completing treatment. The study endpoint was when all patients had completed the study care pathway or had dropped out.

Analysis of data:

We have summarised study data as means (standard deviations), with t tests or chi squared tests used, respectively, to compare between-group baseline parameters. The outcomes from the participant flows were assessed by chi squared and non-parametric significance testing. Since this was a feasibility study, no sample size calculation was performed.

Data collection

Baseline information on age, sex, concomitant medication, co-morbidities and assessment outcomes was collected. Subsequent data was collected on a daily administration log which recorded attendance and any treatment side-effects. Participants completing treatment were invited for a blood test at twelve weeks to ascertain SVR. Recruitment commenced in November 2015 with the study being completed in September 2016.

Process evaluation

A logic model was constructed to explicitly identify targets for evaluation and data collection and is reported elsewhere (Radley et al, 2017). The evaluation examined the processes involved with effectiveness of implementation (Murray et al, 2010). Semi-structured interviews were conducted with (i) 6 service users and (ii) 8 professionals taking part in the study, with all 8 pharmacies represented. The service users who had completed treatment or who had been asked to attend for assessment blood tests were interviewed where possible. Interviews were conducted using topic guides developed in line with the research aims and programme theory. All interviews were recorded as digital audio files and transcribed in full for thematic analysis (Richie and Spencer, 1994). Transcripts were inductively analysed to identify themes emergent from the interviews. These data contributed to the assessment of feasibility and acceptability

(including barriers and facilitators), that had been gained from this and previous work (Radley et al, 2016, 2017).

Resource utilisation of conventional and pharmacist-led pathways

The stages and inputs contained within the conventional treatment pathway were defined through discussion and agreement within the multi-disciplinary team. The stages and inputs contained within the pharmacist-led pathway were defined by the study protocol and reviewed and agreed by the study team.

Cost collection methods

NHS Reference costs, published micro-costing studies, and Personal Social Service Research Unit costs (PSSRU) (Shepherd et al, 2007), were used for the unit costs of managing patients while on treatment.

Monitoring costs refer to the costs of monitoring the patient while they are treated with DAA therapy. Monitoring unit costs were predominantly taken from a micro costing (NHS Reference Costs, 2015) and were inflated to 2014/2015 costs using the Hospital and Community Health Services (HCHS) Pay and Prices Index (Stevenson, 2012 et al). NHS Reference Costs were also consulted as a possible source for this analysis. Although these sources were broadly aligned, more detailed costing data was available, which was essential for this analysis (NHS Reference costs, 2015; Curtis and Burns, 2015).

The unit costs used to estimate the total monitoring costs and service costs for each pathway are displayed in Table 4. Service costs refer to the costs of services (e.g. pharmacist time, nurse time, consultant time) provided to the patient while they are treated with DAA therapy. Unit costs were predominantly taken from PSSRU Unit Costs of Health and Social Care 2015. Unit costs are calculated from NHS reference costs and have been uprated using the HCHS pay & prices inflator (Shepherd et al, 2007).

Assessment of pathway costs

Using the pathway map, monitoring and services costs were summed to cost both the conventional and Pharmacy Pathway. Service unit costs were multiplied by the staff time taken to complete that activity to provide the cost per activity.

RESULTS

Baseline parameters:

There was no significant difference between the age distributions of participants in the conventional pathway (m=38, sd = 7) and in the pharmacist-led pathway (m=37, sd = 8); t (504) =1.65, p=0.100 (Table 1). Chi Square testing showed no significant differences for sex (p<0.4) or the hepatitis C test status parameters between the two participant groups

(p<0.7). The testing and treatment status of both groups at baseline were compared. Mann Whitney U Testing demonstrated no significant differences between the hepatitis C testing parameters ($U_{stat}>U_{Crit}$ α=0.05).

Recruitment and participant flow:

Of 506 patients attending the 8 pharmacies for OST, 175 were identified as having no record of a previous test (35%) for HCV (Table 2) through a data linkage exercise linking OST prescription records with laboratory testing records. Pharmacies randomised to the conventional pathway obtained 58 DBST from 244 patients in receipt of OST (24%). Of these, 15 new reactive tests and 33 new negative tests were identified. The pharmacists also tested 2 participants who were known positives and repeated tests on 8 participants who had been tested in the last twelve months.

Within the pharmacist-led pathway, 94 DBST were obtained from 262 patients in receipt of OST (36%). Of these, 26 new reactive tests and 54 new negative tests were identified. The pharmacists also tested 4 participants who were known positives and repeated tests on 10 participants who had been tested in the previous twelve months. The difference between these variables was significant (p<0.003). Participants in the pharmacist-led pathway were more likely to take a DBST.

Variability in uptake of testing per site was also assessed to evaluate the relationship between number of tests and numbers of OST patients attending each pharmacy (Table 3). A significant difference was identified between pharmacies in the conventional pathway (p<0.002). A significant difference was also identified between pharmacies in the pharmacist-led pathway (p<0.00002). The uptake of testing of OST patients was therefore shown to vary significantly between different pharmacies participating in the trial in both pathways.

Outcomes from testing and treatment:

When a DBST was found to be reactive, participants had either to attend an appointed clinic in the conventional pathway or attend a local phlebotomy service in the pharmacist-led pathway (Table 2). Of the participants referred through the conventional pathway, six from fifteen patients attended at clinic for assessment (27%). Of the participants assessed for treatment in the pharmacist-led pathway, twenty from twenty six patients attended for assessment blood tests (77%). The difference between these variables was significant (p<0.002). Participants in the pharmacist-led pathway were more likely to proceed through the assessment for treatment. Of note, a larger number of genotype 3 patients were seen in the pharmacist-led arm, than the conventional pathway arm (7 versus1), and

these patients were therefore unable to proceed to treatment in this study. A number of reasons for exclusion from treatment were responsible for patient attrition from the pathways, including spontaneous clearance of HCV and identification of a genotype 3 HCV infection.

In this study, one participant completed treatment through the conventional pathway and three patients completed treatment through the pharmacist-led pathway. A flow chart of patient disposal is presented in Figure 1

Process evaluation

Interviews were held with participants who had either completed the pathway or who had tested positive but not yet attended for assessment blood tests. Examples of quotations are set out in Figure 2.

How did participants feel about treatment in pharmacies?

The transcripts of participant interviews demonstrated positive perceptions of treatment in pharmacies. Interviewees clearly thought that pharmacies were a good place to receive care and valued the positive relationships built with pharmacy staff. Lack of money meant travelling to a local hospital was a barrier to clinic attendance. Pharmacies however were viewed as part of the local community. Participants were apprehensive about experiencing stigma and discrimination if people knew of their HCV infection. Participants noted that treatment with DAAs initially made them feel sick and tired, although this quickly faded. On completion of the course of treatment participants expressed positive views about their future and described plans to move their life on.

What feedback on implementation was received from staff?

Interviews were held with a member of staff from each pharmacy in both pathways. Both pharmacists and pharmacy support staff were interviewed. Examples of quotations are found in Figure 2.

Staff interviewees had clear views about what factors led to successful implementation. Staff considered that strong leadership and involving all the pharmacy team were necessary prerequisites for success. The intervention was less successful in areas where this was lacking. The degree of enthusiasm for new roles and positive relationships with patients were also important. Where the testing and treatment service was seen as the sole responsibility of the pharmacist, the pharmacies managed to complete fewer tests. Pharmacist availability was a limiting factor where this occurred. Less tests were completed in pharmacies were the staff felt under pressure because of dispensing work load. Where the service was seen as a team responsibility, the service was more

successful and the intervention was able to cover a greater number of patients. Positive relationships with patients were a key factor. Where these relationships were weaker, the acceptance of testing and the progress into treatment was less successful. In pharmacies with strong patient relationships, the service was seen as part of the range of ways that the health of the patients was improved. There were some initial anxieties expressed about potential contact with infected blood, but respondents said that these fears soon faded. The patient assessment was felt to be straightforward and easy to accomplish.

Staff appreciated that participants often needed time to come around to the idea of being tested and entering treatment. The need for off-site phlebotomy was recognised as a weakness in the pharmacist-led care pathway.

Resource utilisation of conventional and pharmacist-led pathways

The different levels of input and intervention in the conventional and pharmacist-led pathways are demonstrated in Figure 3. The total cost of the conventional Pathway was estimated at £933 (£643 service cost, £290 monitoring cost), and the cost of the Pharmacy Pathway was estimated £238 (£143 service cost, £95 monitoring cost) (Table 4). Therefore, utilising solely the pathway costs, the difference in the cost per patient was £695 (£499 service cost, £195 monitoring cost). The costs associated with the pharmacy setting are around one quarter of the cost of treating a patient in a conventional setting (assuming the same cost of DAA treatment). In terms of staff capacity, the pharmacy pathway model uses four hours less service resources than the conventional pathway (6.66 hours with conventional pathway versus 2.66 hours with pharmacy pathway).

DISCUSSION

Main study findings

This feasibility study provides evidence that community pharmacies can successfully provide DBST to patients attending for OST and that progression to treatment is feasible. More participants accepted a DBST in a pharmacist-led pathway than in the conventional pathway, where there was no requirement to attend a hospital clinic for treatment. Interviews with participants identified a number of explanatory factors for this. This study found that more participants undertook assessment for treatment in the pharmacist led pathway, where the care pathway was delivered entirely in the pharmacy. Both patient and staff experiences and views demonstrated how the pharmacist-led pathway overcame some of the barriers that prevent people prescribed OST accessing testing and treatment.

Strengths and weaknesses of the study

The criteria set out for evaluating the success of the feasibility trial included whether people who receive OST for pharmacies could be recruited to the study; whether pharmacies could successfully complete all elements of the testing and treatment pathway; which elements of the pathway work well and which elements are less successful; to make an estimate of the effect size in terms of how many participants complete each stage of the pathway (Arain 2010). The study has provided evidence that these criteria can be met: OST patients can be recruited and pharmacies can guide patients through all stages of the pharmacist-led pathway.

The need to attend for off-site phlebotomy led to some loss of potential patients in the pharmacist-led pathway and this weakness should be addressed in the design of the final pathway for full trial, with perhaps the inclusion of peripatetic phlebotomy services visiting pharmacies. This study demonstrated that three participants could access treatment in the pharmacist led pathway compared to one participant in the conventional pathway. However, a series of further aspects also provide encouragement that a significant effect size is present, including the reduced losses at clinic attendance stage in the pharmacist-led arm. Notably, demonstration of a larger effect size in the pharmacist-led arm was impaired because of a larger proportion of patients spontaneously clearing infection and a great number of genotype 3 patients being identified in this arm, which at the time of the study could not be treated with interferon free regimens.

Some variation in uptake was observed between pharmacies in both pathways. Additional factors may explain this variation, such as the degree of enthusiasm of the pharmacy staff for new roles, the relative burden of dispensing workload in the pharmacy and the leadership shown by the pharmacist. This variance may be addressed through growing acceptance of this service as part of what a pharmacy should offer.

A further limitation is the access of pharmacies to electronic laboratory results services. Although, these are now being implemented into pharmacies in some areas, this resource is not yet widely available. The consequence of this, as identified in this study, was that some patients received duplicate blood tests. Additional variables such as length of time of OST and the dispersal of co-morbidities and BBV co-infection may also act as confounders. The use of pharmacies as study sites precluded assessment of medical notes to assess these factors systematically, but the DBST taken from clients assessed Hepatitis B and HIV co-infection, as well as HCV. Collection of data on length of time on OST will be build into the design of the full trial. The study protocol required that co-infected

patients were directly referred to the standard care pathway. A further large scale study is now being implemented to fully assess the potential of this pathway.

Interpretation of findings

Previous pilot work from this programme has explored the context for delivery and the mechanisms that may lie behind the outcomes observed (Radley, 2017). Contextual factors have previously been identified by other authors, including: expectations and experiences of stigma and discrimination; fears about confidentiality; the limited horizons of people receiving OST and the poverty they experience (Harris et al 2013, Wade et al 2016). Identified mechanisms that may influence uptake included the presence of established relationships with pharmacy staff; a pre-existing reason for attending the pharmacy for OST and the proximity of the pharmacy within the local community. The work undertaken in this study, has confirmed that the local nature of the pharmacy and the pre-existing reasons for attendance are key mechanisms in recruitment for testing and that good quality relationships between pharmacy staff and participants, supports recruitment (Edlin et al 2005). The barriers to completion of either of the care pathways were also confirmed: that participant may be anxious about what the results might mean for them, or mistrustful of the way they might be treated. Although the pharmacies provided a familiar environment within their local community, hospitals represented an unfamiliar setting. The health literacy required to navigate the journey from the participant's normal setting to attend multiple hospital-based appointments was a significant barrier (Arora et al 2011). For the pharmacist-led arm of the study, even the attendance at an external venue for a single phlebotomy appointment was a significant barrier, leading to patient loss from the pathway.

Treatment pathways that increase access and uptake of treatment of DAAs are required. Uptake of testing and treatment is currently low (Weissing, et al, 2014) and authors across the world have identified many common barriers that must be overcome by potential patients to treat the HCV infection (Wade et al 2016, Konerman and Lok, 2016). There are identified deficiencies in the amount of screening and diagnosis undertaken for at-risk populations, as well as improvements required in access to treatment initiation and clinical monitoring (Artenie et al, 2015): The infrastructure to deliver sufficient treatment to enable eradication is not generally available or of sufficient scale (Leask and Dillon, 2016). People who inject drugs may find it difficult to consistently attend the medical clinics that are the mainstay of standard of care (Papatheodoridis et al, 2016). Delaying

treatment because of funding problems risks patients being lost to follow-up (Fox and McCombe, 2016).

Creating the complex interventions necessary to eliminate HCV requires that well-designed cross-disciplinary programmes are put in place (Suther and Harries, 2016) using a variety of strategies to increase screening, testing and diagnosis (Brouard et al, 2015). The delivery of HCV testing and treatment through community-based care pathways has been shown to be feasible (Coats and Dillon, 2015).

There have been a number of different routes chosen to provide primary care-based treatment pathways. A targeted general practice-based screening intervention has been recommended, since low diagnostic yields limited the effectiveness of non-targeted approaches (Anderson et al, 2009). Current work aims to produce a scalable general practice model (Roberts et al, 2016). Community-based, nurse-led care for HCV has shown been shown to be effective (Wade et al, 2015). The change away from interferon-based regimes should improve the proportion of people who are willing to undertake treatment (Lewis et al, 2016).

As well as the benefits that arise from harnessing the established OST care system already implemented in the pharmacy, such as improved regime adherence, there are further benefits gained through developing a new pathway designed to take advantage of DBST and the reduced burden of DAA treatment. The lower cost of primary care premises compared to hospital clinics as well as the simplified testing and monitoring requirements, is responsible for the lower estimated cost of the pharmacist-led pathway. These lower costs are likely to prove favourable even if current hospital-based standard of care pathways are also simplified and made more efficient. Although the conventional care pathway reported in this study required twelve attendances to complete treatment, other authors have reported pathways with up to eighteen stages (Arora 2011) With current pathways, the use of DAAs is cost-effective at all stages of liver disease (Leidner et al, 2015, Liu et al, 2012). With primary care based care pathways capable of recruiting greater numbers of people with HCV infection, cost-effectiveness of these medicines may increase further (Bennett et al, 2015). A coordinated programme delivered through a managed care network has increased the numbers of people accessing treatment and shortened the time for people with HCV infection to achieve an SVR (Tait et al, 2016). A multi-disciplinary approach to care has been demonstrated to improve care.

CONCLUSIONS

This feasibility study provides further evidence that service users prescribed OST can access testing and treatment through a pharmacy. Use of a pharmacist-led pathway may remove some of the barriers that prevent OST patients accessing testing and treatment through conventional pathways.

A number of the identified barriers to the uptake of testing in this study were overcome through the local availability of the pharmacies and positive relationships with pharmacy staff. The use of community pharmacy delivered care has the potential to contribute to elimination of HCV in the United Kingdom. Further work to evaluate the outcomes associated with this service configuration is now on-going (NHS Research Authority, 2016).

The references to this paper are located in the manuscript provided in Appendix 9.5

Table 1: Baseline characteristics of trial population by group allocation

Characteristic	Conventional pathway (%)	Pharmacist-led Pathway	
Participants (n)	244	262	
Male	165 (68)	167 (64)	
Female	79 (32)	95 (36)	*p*=0.358
Age (years)			
20-24	3 (1)	7 (3)	
25-29	22 (9)	40 (15)	
30-34	65 (27)	64 (24)	
35-39	56 (23)	55(21)	
40-44	44 (18)	55(21)	
45-49	36 (15)	26(10)	
50-54	14 (6)	8(3)	
55-59	4 (2)	4(2)	
60-64	0	2(1)	
65-69	0	1	*p*=0.100
Hepatitis C Status			
Continued Follow-Up in Treatment	34 (14)	32 (12)	
Previous SVR Completed Treatment	20 (8)	21 (8)	
Last Test Negative	89 (36)	90 (34)	
No Record of Previous Test	80 (33)	95 (36)	
Referral, Did Not Attend	4 (2)	10 (4)	
Attended, Did Not Complete	14 (6)	14 (5)	*p*=0.622
Positive Test, No Referral	3 (1)	0	-

Table 2: Participant Flow and outcomes

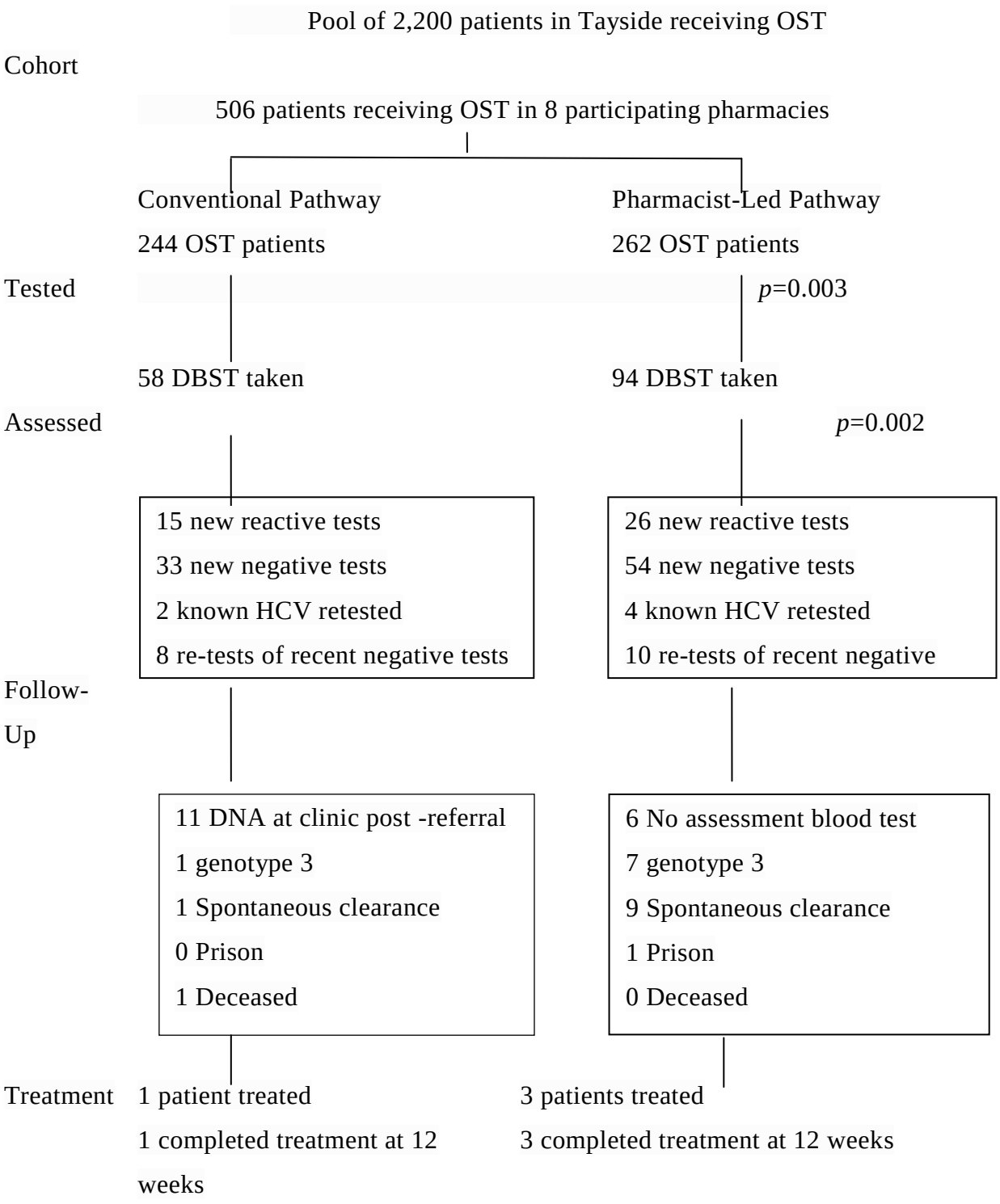


Table 3 Patient Outcomes – Uptake of testing and treatment by pharmacy site

Site	No. Patients	No record of previous test	DBST (%)	Known positives	Repeat test	New positives	New negatives
1	68	25	11 (16)	0	0	0	11
2	76	26	21(28)	2	2	7	10
3.	62	19	9(15)	0	3	2	4
4.	38	10	17(45)	0	3	6	8
Totals	244	80	58(24)	2	8	15	33
5	84	39	43 (51)	1	1	10	31
6	51	19	7(14)	0	0	2	5
7	86	21	20(23)	3	6	5	6
8	41	16	24(59)	0	3	9	12
Totals	262	95	94(36)	4	10	26	54

Figure 1: Percent Attrition of Patients with Reactive Tests for Conventional and Pharmacist-Led Pathways

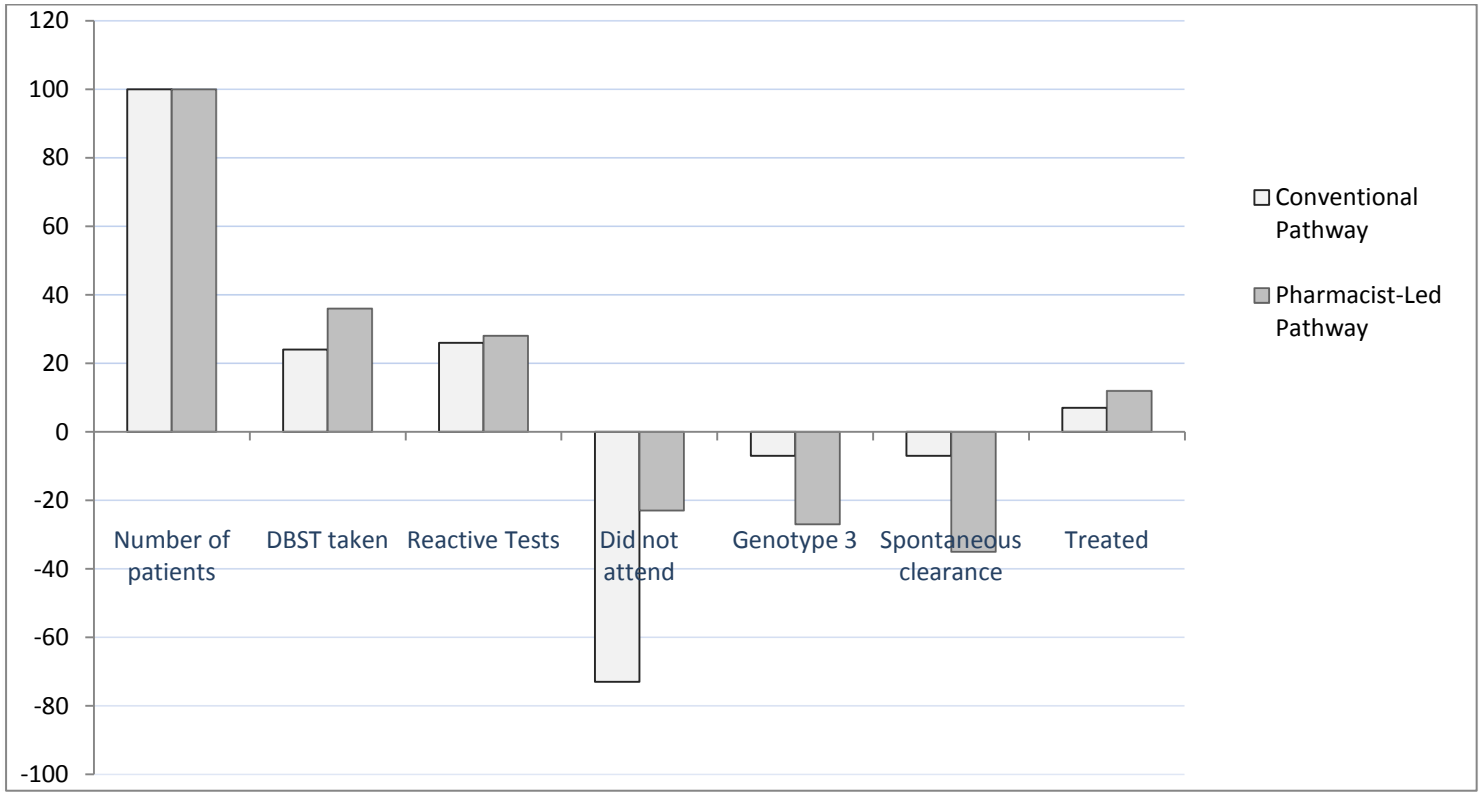


Figure 2: Examples of quotations from service users and staff participants

Service Users

How did Hepatitis C affect your life?

"I already knew I had Hepatitis C, I got diagnosed with it more than 10 years ago. I had always been waiting for the time ... my life just never seemed to get to a point where it was stable enough to do it" Participant 1, male

"A couple of years ago I said to one of my pals there wus somethin' wrang wi' us, I was just tired, no strength to go any place" Participant 2, female

What was your experience of treatment in the pharmacy?

"I recognise that this is a big plus, being able to get a tablet every day at the chemist is so ease, so convenient". Participant 4, male

"When you got to the hospital sometimes you feel like you are being treated differently and I just found that in here(in the pharmacy) it was a more warmer environment and friendly" Participant 6 male

Has completing treatment made any differences to you?

"But I honestly feel different; I feel like my old self ken, I feel better" Participant 1, male

"Going forward now it more just that, eh I want to go back to college and get into youth work if I can. I have a prospectus as home, so my future .. what I see is me hopefully doing something along lines". Participant 2, Female

Staff

How did you feel about taking part in the study?

"I was quite excited about it, quite looking forward to doing it, it was something quite different for pharmacies to do, we would get more involved with the methadone patients, so I was very interested and keen for it". Staff Member 7, Female

How did you manage the participants and help them to complete the pathway?

"you build up your conversations and your style of conversations, the more you gain in confidence, the better the client feels and they also like to understand that we are learning and developing with them, they like to feel part of something too". Staff member 3, Female

"We did try quite a few times to get him to go but he kept said he would be going, in fact I think once he said he had gone but he wasn't able to get tested, but I don't know if that's true or not". Staff Member 5, Male

Figure 3: Conventional and Pharmacist-Led Pathways

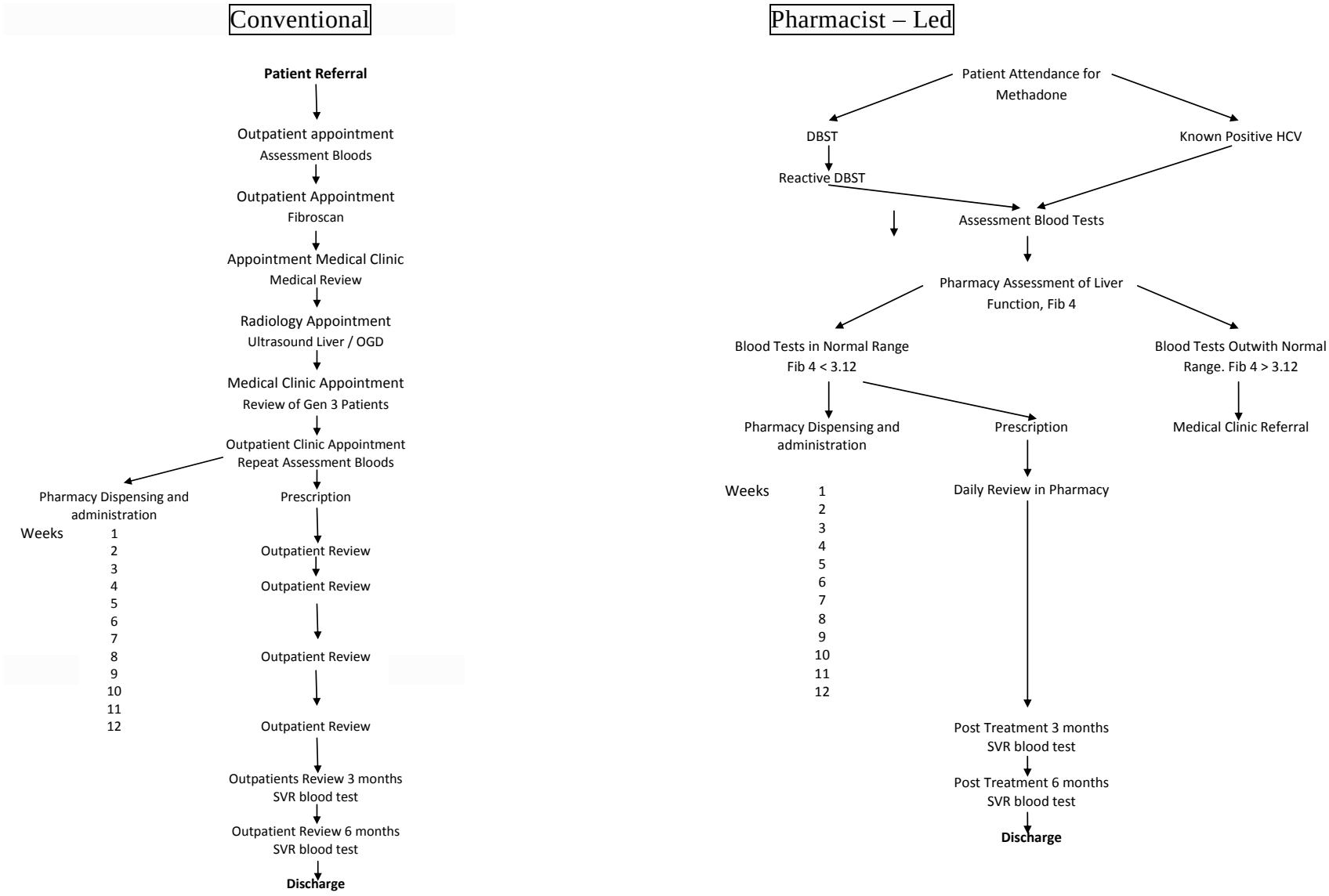


Table 4: Monitoring costs and service costs -Conventional Pathway Costing Results

Stage	Reason	Activity (Estimated Staff Time hrs)	Cost (per activity)
1	Dried Blood Spot Test	Specialist Nurse (0.33)	£41
		Dried Blood Spot Test	£40
2	Outpatient appointment	Specialist Nurse (0.66)	£83
		Liver Panel	£5
3	Outpatient Appointment	Ultrasonographer (0.5)	£20
		Fibroscan	£55
4	Appointment Medical Clinic	Consultant (0.5)	£69
		Liver Panel	£5
5	Radiology Appointment	Ultrasonographer (0.5)	£20
		Ultrasound Liver	£63
6	Medical Clinic Appointment	Consultant / Registrar (0.33)	£24
7	Outpatient Clinic Appointment	Specialist Nurse (0.5)	£63
		Liver Panel	£5
8	Prescription	Pharmacist Prescriber (8a) (0.5)	£36
9	Outpatient Review	Specialist Nurse (0.33)	£41
		Liver Panel	£5
10	Outpatient Review	Specialist Nurse(0.33)	£41
		Liver Panel	£5
11	Outpatient Review	Specialist Nurse (0.33)	£41
		Liver Panel	£5
12	Outpatient Review	Specialist Nurse (0.33)	£41
		Liver Panel	£5
13	Outpatient Review	Specialist Nurse (0.33)	£41
		SVR	£50
14	Outpatient Review	Specialist Nurse (0.33)	£41
		SVR	£5-
15	Discharge	Specialist Nurse (0.33)	£41
Total Pathway Cost			£933
Service Cost			£643
Testing Cost			£290

Pharmacy Pathway Costing Results

Stage	Reason	Activity (Estimated Staff Time hrs)	Cost (per activity)
1	Pharmacy Attendance for Methadone	Pharmacist (0.33)	£17
2	Dried Blood Spot Test in Pharmacy	Pharmacy Assistant (0.33)	£3
		Dried Blood Spot Test	£40
3	Assessment Blood Tests	Specialist Nurse (0.33)	£25
		Liver Panel	£5
4	Patient Assessment in Pharmacy	Pharmacist (0.5)	£25
5	Prescription	Pharmacist Prescriber (band 8a) (0.5)	£25
6	Outpatient Review (SVR test)	Specialist Nurse (0.33)	£25
		SVR	£50
7	Discharge from Service	Specialist Nurse (0.33)	£25
Total Pathway Cost			£238
Staff Cost			£143
Testing Cost			£95

5.2 Clinical effectiveness of pharmacy-led versus conventionally delivered antiviral treatment for Hepatitis C in patients receiving opioid substitution therapy: A study protocol for a pragmatic cluster randomised trial SuperDOT-C

The following paper is a verbatim copy of Radley A, de Bruin M, Inglis S, Donnan PT, Dillon JF. BMJ Open 2018. DOI: 10.1136/bmjopen-2017-021443

ABSTRACT

Introduction: Hepatitis C Virus (HCV) infection affects 0.7% of the general population, and up to 40% of people prescribed Opioid Substitution Therapy (OST) in Scotland. In conventional care, less than 10% of OST users are tested for HCV and less than 25% of these initiate treatment. Community pharmacists see this group frequently to provide OST supervision. This study examines whether a pharmacist-led 'test & treat' pathway increases cure rates for HCV.

Methods and Analysis: This protocol describes a cluster randomised trial where 60 community pharmacies provide either conventional or pharmacy-led care. All pharmacies offer dried blood spot testing (DBST) for HCV. Participants have attended the pharmacy for OST for 3 months; are positive for HCV genotype 1 or 3; not co-infected with HIV and/or hepatitis B; no decompensated liver disease; not pregnant. For conventional care, pharmacists refer HCV positive participants to a local centre for assessment. In the pharmacy-led arm, pharmacists assess participants themselves in the pharmacy. Drug prescribing is by nurse prescribers (conventional arm) or pharmacist prescribers (pharmacy-led arm). Treatment in both arms is delivered as daily modified directly observed therapy (DOT) in a pharmacy. Primary trial outcome is number of sustained viral responses (SVR) at 12 weeks after treatment completion. Secondary trial outcomes are number of tests taken; treatment uptake; completion; adherence; re-infection. An economic evaluation will assess potential cost-effectiveness. Qualitative research interviews with clients and health professionals assess acceptability of a pharmacist-led pathway.

Ethics and Dissemination: This protocol has been ethically approved by the East of Scotland Research Ethics Committee 2 (15/ES/0086) and complies with the Declaration of Helsinki and principles of Good Clinical Practice. Informed consent is obtained before study enrolment and only anonymised data is stored in a secured database, enabling an

audit trail. Results will be submitted to international peer-reviewed journals and presented at international conferences.

ClinicalTrials.gov Identifier: NCT02706223

Protocol version 3.0. Date 27 May 2016

Strengths and limitations of this study

Real world study developed using the Medical Research Council (MRC) Guideline on complex interventions

Potential to provide answers to an extremely topical question around approaches to eliminate a disease, in line with a World Health Organisation (WHO) target.

Utilises a community pharmacy-based pathway in NHS Scotland, but not wider primary care systems

Relies on close and integrated working between a specialist hepatitis service and community pharmacy services

BACKGROUND

Hepatitis C (HCV) is a blood-borne viral infection causing liver disease. Around 0.7% of the Scottish population are chronically infected with HCV [1]. Patient outcomes from HCV infection vary, with 25% clearing the infection spontaneously and the remainder becoming chronically infected, risking development of cirrhosis and hepatocellular carcinoma [2]. A recent Public Health England report highlighted that less than half of those infected with HCV have been identified, and of those identified less than 3% of those known to be infected with HCV are being treated [3]. The greatest risk of acquiring the virus in the UK is through injecting drug use [4] and evidence suggests around 40% of people in Scotland receiving Opioid Substitution Therapy (OST) have HCV infection [5]. Only a small proportion of this high-risk and vulnerable population are receiving adequate treatment, despite having daily healthcare interaction with a pharmacist and the availability of a curative intervention with widely available Direct Acting Antiviral (DAA) medication [6].

The conventional care pathway in the United Kingdom recommends that patients with a history of intravenous drug use, or those currently prescribed OST, should be offered HCV testing annually [3]. Testing may be available from their GPs, drug workers, drug agencies, social workers, community pharmacies and needle exchanges [7]. Once diagnosed, patients can be referred to established treatment pathways, usually based

around hepatology teams in secondary care. In these established treatment pathways, less than 10% of the OST population are tested for HCV annually. Of those tested, at most 25% start treatment in one of the dedicated centres and 70-80% successfully complete treatment, with treatment failure primarily caused by non-adherence and non-persistence to treatment [8]. Similar patterns are observed in other countries [9]. The inefficiency of established treatment pathways leads to increased preventable deaths from HCV and viral transmission within the injecting population [10].

A variety of reasons may explain the low rates of HCV testing, treatment uptake, and treatment completion. People who inject drugs (PWID) may encounter a number of barriers that prevent them from accessing care, including perceptions and experience of stigma and discrimination, issues with the organisation of care and the treatment policies of providers or payers [11]. There are identified deficiencies in the extent of screening and diagnosis of at-risk populations, as well as the need to simplify pathways to enable treatment initiation and clinical monitoring [12]. People who inject drugs may find it difficult to consistently attend medical clinics [13].

The WHO has set an ambitious goal to eliminate HCV as a public health threat by 2030 [14]. Creating the complex interventions necessary to eradicate HCV requires that well-designed cross-disciplinary programmes are put in place using different strategies to increase screening, testing and diagnosis [15]. Strategies that demonstrate increase testing and treatment uptake include the provision of integrated HCV care pathways; with drug use and psychiatric services delivered by a multidisciplinary team, and with case management services [16]. The delivery of HCV testing and treatment through community-based care pathways has also been shown to be feasible and DBST has been demonstrated to increase the uptake of testing from high-risk populations [17]. Hence, a more central role in the treatment of HCV for community-based pharmacists who are seeing these clients on a daily basis, could – in theory – lead to increased HCV treatment success rates through higher HCV testing, treatment uptake, adherence, and treatment completion rates.

In preparation for the current trial investigating the clinical benefits of pharmacy-delivered HCV treatment, pilot work was undertaken guided by the MRC theoretical framework for developing and evaluating complex interventions [18]. Initial work involved using a co-production approach in partnership with OST patients. This work identified the current experiences of patients in accessing HCV testing and treatment and in accessing OST in pharmacies [19]. The attributes of an ideal service were identified

and an estimate of potential uptake made [20]. The implementation of DBST in pharmacies was undertaken and the experiences of patients and providers recorded [21]. A pilot trial has been undertaken to test each stage of the pharmacy-led care pathway and to look for confirmation that an appropriately powered definitive multicenter randomised controlled trial would be feasible [22]. The PRECIS-2 tool was used to assess that the design decisions were concordant with the purpose of the trial (Supplementary file 1) [23].

The aim of this research is to examine the impact of pharmacy-delivered HCV treatment on HCV treatment success rates amongst OST users. Our research questions are:

Trial

(1) Does a community pharmacist-led HCV treatment pathway increase treatment success rates (sustained virological response, or SVR) compared to the conventional pathway?

(2) Does a community pharmacist-led HCV treatment pathway lead to a higher uptake of HCV testing?

(3) Does a community pharmacist-led HCV treatment pathway lead to a higher uptake and completion of HCV treatment?

(4) Is adherence and persistence to HCV therapy in the pharmacy setting similar to that in the Conventional pathway?

(5) What is the re-infection rate at 12 months after end of treatment in all patients with SVR, and for the pharmacist-led pathway compared to the conventional pathway?

Health Economics Study

(6) Is the pharmacist-led pathway potentially a cost-effective method of testing and treating HCV in people prescribed OST?

Qualitative Study

(7) Is the pharmacist-led pathway an acceptable way to offer testing and treatment for people prescribed OST infected with HCV and are there any unexpected consequences?

METHODS:

Design

Super DOT-C is a cluster randomised trial of pharmacy-led anti HCV therapy versus conventional care in HCV infected patients attending community pharmacies. Sixty pharmacies will be enrolled to this study across 5 hubs in Health Boards in NHS Scotland. Pharmacies (and thus their patients) participating in the trial will be randomly allocated to conventional care pathway or the pharmacy-led pathway.

Pharmacies at each site are randomised into two groups: conventional care and pharmacist-led care. Randomisation will be carried out using http://www.randomization.com. The subjects are randomized into one block along with the number of subjects per block/number of blocks and (case-sensitive) treatment labels. The pharmacies in each hub provide the level of randomisation, so patient allocation is dependent on the pharmacy attended.

Eligibility Criteria

Eligible pharmacies are community-based, offer DBST for HCV by trained pharmacy staff in line with approved practice in their particular NHS board and have at least 30 patients on OST to ensure adequate recruitment. Patient inclusion criteria are having HCV Polymerase Chain Reaction (PCR) positive to genotype 1 or 3, are OST users and willing to have their pharmacists supervise their antiviral drug use. Patient exclusion criteria are having another genotype than 1 or 3, evidence of current or previous decompensated liver disease, Human Immunodeficiency Virus (HIV) infection, surface antigen of Hepatitis B Virus (HBV) HBsAg positive with detectable HBV DNA, aggressive or violent behaviour towards the pharmacist, being pregnant, and not being able to provide informed consent.

Interventions:

Medication provided

The anti HCV treatment provided in both pathways is identical, i.e:

For HCV genotype 1 sofosbuvir/ledipasvir for 8 weeks

For HCV genotype 3 sofosbuvir/daclatasvir for 12 weeks

Study Site Staff Training

Staff from each study site will receive training on Good Clinical Practice, quality control, use of study documentation, ensuring common practice, and consenting participants. In addition training to establish testing for blood borne viruses is provided and information on hepatitis C and its treatment is provided. Staff in the pharmacy-led arm are trained on how to interpret laboratory bloods and to perform a Fib4 calculation [24].

Table 1: Treatment pathways: similarities and differences

	Conventional care	Pharmacy pathway	Contrast
Hepatitis C Virus testing	Opportunistic HCV testing on presentation for OST therapy	Opportunistic HCV testing on presentation for OST therapy	The same procedure is provided in each of the study arms
Hepatitis C Virus test confirmation	Test result is communicated and - if positive – referred for assessment in local treatment centre	Test result is communicated and – if positive - assessment directly undertaken in the pharmacy	Assessment for treatment is carried out at the pharmacy when the participant visits to obtain OST, not at a different site with a different provider
Treatment initiation	Suitable patients are prescribed treatment by a nurse prescriber at the local treatment centre and access treatment through DOT at their pharmacy	Suitable patients are prescribed treatment by a pharmacist prescriber and access treatment through DOT at their pharmacy	Treatment initiation is carried out at the pharmacy and not at a different site with a different provider
Treatment monitoring	Treatment monitoring is carried out by the specialist team in their clinic	Treatment monitoring is carried out at the pharmacy	Treatment monitoring is carried out at the pharmacy not at a different site. Monitoring in the conventional pathway requires additional clinic visits
Treatment completion	Sustained Viral Response testing is carried out by DBST at the pharmacy	Sustained Viral Response testing is carried out by Dried Blood Spot Testing at the pharmacy	The same procedure is provided in each of the study arms

Conventional Care Pathway

At the start of the pathway pharmacists will opportunistically discuss HCV infection with their OST patients. The pharmacist will record on a screening log which of the OST patients attending the pharmacy they have approached. Those with unknown HCV status will be offered testing using a DBST in the pharmacy [25]. Patients identified as having HCV antibodies will have a post-test discussion with the pharmacist. During this discussion the pharmacists will obtain informed consent and explain about HCV treatment using a standard infographic (supplementary file 2). Next, the pharmacist will offer them referral to the conventional care pathway for assessment and treatment at a local treatment centre. Information will be provided verbally and by offering standard leaflets about HCV. If the patient attends an appointment at one of the local treatment centres, a member of the specialist hepatitis team will invite the patient to undertake assessment for treatment for HCV. Assessment comprises of a pre-treatment checklist of medical co-morbidities, medical history, and concomitant medication to look for drug-drug interactions. The patient will undergo phlebotomy in the local treatment centre to check full blood count, urea and electrolytes, liver function testing, including markers of liver fibrosis [24] (Fib4, APRI, AST:ALT ratio) and viral parameters (genotype and load), as assessment for treatment. Patients who are referred for assessment and treatment will be managed according to the standard local treatment pathway. Daily supervised OST treatment is delivered by the pharmacy, in which the doses of methadone or buprenorphine are provided by the pharmacy staff, who observe consumption. In both arms of the study DAA treatment is delivered jointly with OST in their normal pharmacy; which would qualify as DOT during weekdays, although at weekends patients usually self-administer. Prescriptions will be provided by a nurse prescriber and dispensed at the participant's normal pharmacy. For doses that patients have to self-administer and the weekend doses when there is no OST distribution, the pharmacist and patient will make a brief if-then action plan (an implementation intention) and coping plan (to overcome anticipated barriers) [26]. The study related data collection will be undertaken by the specialist hepatitis team.

Pharmacist-Led Pathway

Potential participants are offered testing, recruited and consented as in the conventional pathway. In the pharmacy-led pathway however, the pharmacist will offer them anti-HCV therapy delivered solely within the pharmacy. The patients who decline study

participation will be entered in the screening log. For the patients who do consent, the pharmacist will complete a pre-treatment checklist of medical co-morbidities, medical history, and concomitant medication to look for drug-drug interactions. The patient will undergo phlebotomy in the pharmacy for safety blood tests, as in the conventional pathway and the pharmacist will assess this information to determine suitability for treatment.

If there are no contra-indications to therapy, the patient will commence the treatment. In patients where there are contraindications or queries about suitability, the pharmacist will contact the central clinical co-ordinator for advice. The pharmacist-led pathway requires an assessment which includes identification of concurrent specific medical conditions, screening of safety bloods, calculation of a Fib-4 score, assessment of interacting concurrent medication and assessment of factors likely to impinge on treatment compliance. Potential participants with a FIB-4 score of > 3.25 are referred on to the Conventional Care Pathway for review. The Pharmacist-led Pathway therefore excludes this group from being entered into the trial. Instead, they are assessed for treatment through the Conventional Care Pathway where they are reviewed in hospital by a medical consultant who decides if it is safe to proceed with treatment and if yes, may select different drugs'. Unsuitable patients are therefore referred to the conventional pathway for assessment outside the study and provided with standard clinical care. Prescriptions for treatment will be provided by pharmacist prescriber.

Each time that patients pick up their medication from the pharmacy, a daily log is completed, recording any occurrence of side-effects or adverse events.

Participants who do not attend the pharmacy for seven consecutive days will be discontinued from the study since they will be deemed to have discontinued their course of DAA treatment and will have had their OST prescription suspended.

Participants are likely to be retained within the study through the mechanism of daily attendance for receipt of supervised OST; this is a powerful mechanism making people return to the pharmacy. It is intended that data will still be collected on participants who may not complete their course of treatment, since partial completion may produce an SVR also.

The primary study outcome (SVR 12 weeks after treatment completion) is assessed by DBST in the pharmacies for both study arms.

Outcomes and measures

The denominator for the outcomes on treatment uptake is the number of people using OST at the pharmacies participating in the respective arms. For the primary outcome, the numerator will be the number of patients with Sustained Viral Response at 12 weeks post treatment completion (SVR12) after allocation to treatment arm, measured through a test for the presence of HCV RNA (polymerase chain reaction).

For the secondary outcomes on treatment uptake, the numerators are the number of patients who (a) undergo HCV testing, (b) initiate HCV treatment, (c) complete the 12-week HCV course, (d) number of patients with SVR at 12 months (to assess the impact of potential reinfection).

Study schedule

For both arms, screening for HCV by DBST is undertaken prior to recruitment (t_0); participant consent (t_1) is followed by 8 or 12 weeks of treatment according to HCV genotype (t_{12}), 12 weeks post-treatment a final SVR test is taken to determine the study outcome ($t_{endpoint}$)

Sample Size:

Approximately 22,000 patients are prescribed OST across Scotland [26]. Around 85% of these patients receive daily or regular supervision of their OST consumption through one of the 1200 community pharmacies. It is expected that at least 40% of these patients will be infected with HCV, and that around 46% and 48% of infections will be with Genotype 1 and Genotype 3 respectively [9]. The pharmacies acting as cluster sites for this trial have around 1,800 patients attending for supervised OST administration. Sixty community pharmacies based around 5 study sites within Scottish NHS Boards, will be coordinated through the Tayside Clinical Trials Unit (TCTU) of the Tayside Medical Science Centre, University of Dundee.

As the pharmacy-led pathway is a specific population-based intervention, the number of patients on OST treatment at each pharmacy will be the denominator for calculating DBST uptake. The HCV infection status of all the OST patients in the denominator population is not known. National data repeatedly shows approximately 40% of Patients on OST are HCV positive, as this is a randomised trial it can be assumed that the rate of HCV positivity in the OST patients/pharmacies randomised to the pathways should be the same. The study will be powered through rates of HCV therapy offered. Approximately 3% of HCV positive OST patients enter HCV therapy per year via conventional pathways, with 2.5% of the total eligible population achieving SVR per annum. If it is estimated that the new pathway increased this to 15%, a sample in each arm of 141 (2N =

282) will give 90% power at the significance level. The clustered design requires inflation to account for intracluster correlation, so if the average infected subjects per pharmacy is 12, the Inflation Factor for sizes of cluster assuming an intra-cluster correlation of 0.05, is 1. 55. This leads to a need for 2N = 437.

The sample of 60 pharmacies with an average of 30 OST patients per pharmacy gives 1800 OST patients, assuming 40% HCV positive, gives 700 to 800 potential patients for study. This gives significant protection against any changes in baseline SVR success rates, but also against pharmacy drop-outs or local issues that prevent an enrolled pharmacy from participation. This is trial of a pathway so all eligible patients are the denominator for the power calculation, not the patients who actually enter the pathway and are treated.

The randomisation of the pharmacies will be stratified by associated hub centre. The endpoint of the study is the effectiveness of the pathway so any drop-outs are part of the study outcomes, so there is no need to increase the sample size to allow for a dropout rate.

DATA COLLECTION, MANAGEMENT AND ANALYSIS

Analysis of the trial will follow the principles outlined in the ICH E9 ‘Statistical Principles for Clinical Trials’ and carried out by the UKCRC registered Tayside Clinical Trials Unit (TCTU). Prior to data lock an agreed Statistical Analysis Plan (SAP) will be finalised covering the pre-specified statistical analysis.

The primary outcome of SVR will be assessed as a binary outcome for subjects and so will utilise logistic regression modelling. The numerator will be the number of subjects achieving SVR at 12 weeks and the denominator will be total number of patients using OST and having an HCV infection diagnosed at the participating pharmacies.

Additionally results will be expressed as a proportion of the estimated HCV infected subjects on OST. The estimated number of infected patients will be based on national survey data and the empirical rate discovered in the trial (allowing for patients who refuse testing). In order to account for the clustered nature of the trial, a mixed-effects logistic regression model will be performed with the parameter indicator of trial arm in the model and a random parameter to account for within cluster correlation as well as stratified by hub. As all patients will have either achieved SVR or not and we will assume that drop-outs / lost to follow-up are failures, there will be no missing data in the primary outcome. Extra- binomial variability or over-dispersion will be examined in the logistic model and if present alternative modelling such as negative binomial models will be considered.

This will also be adjusted by therapy and genotype; the two factors are interdependent determining length of therapy.

Secondary binary outcomes - will be analysed in the same procedure, initially as intention to treat with all eligible patients as the denominator and then to explore the steps in the pathway by per protocol analysis in particular to analyse on treatment success:

Proportion of HCV tested: within the duration of the study of those attending pharmacy sites for OST, for the conventional and for the pharmacist-led arm

Proportion that initiate HCV treatment within the duration of the study of those identified with HCV, for the conventional and for the pharmacist-led arm.

Proportion that complete the course of those initiating treatment: Multiple logistic regression modelling will explore the patient and pharmacy characteristics that are associated with the secondary outcomes and primary outcome. Patient outcomes considered will be:

-age
-gender
-deprivation,
-employment,
-co-morbidity,
-psycho-social variables assessed.

Pharmacy characteristics considered will be:

-geographic location
-type of pharmacy service
-size of OST population.

Determination of re-infection: As the determination of possible re-infection is an important and stated secondary outcome in this study, all patients will be invited to consent for a further DBS HCV PCR one year after end of therapy or at end of the study, whichever is first. Those patients who achieve SVR will be invited to participate at their pharmacy. People prescribed Opioid Substitution Therapy (OST) are retained in the service for many years, since their progress of recovery and becoming drug-free is slow. In addition, movement out of Dundee, which is relatively geographically isolated, is minimal. We are therefore confident that we can identify all patients still in receipt of a prescription for OST and invite them to be re-tested for Hepatitis C. Since the network of pharmacies providing OST, are also trained to provide testing, we believe this is feasible

Data management

An EXCEL database will be used to hold the study related data. This will be managed and controlled by the coordinating pharmacist in NHS Tayside with site specific data being transcribed from a paper Case Report Form (CRF) formulated in line with the EXCEL database, with the study protocol and in line with the requirements of the investigators. Development and validation of the study database, quality control and extraction of data will be done according to study sponsor procedures. Extracts for analysis will be based on the data tables provided by the study team.

Health Economic Assessment

Economic analysis will be undertaken alongside the trial, utilizing the costs, resource use and effectiveness data generated within the trial. The number of SVRs achieved at the end of the trial will be combined with the cost data to calculate the incremental cost per cure. A longer term analysis incorporating the cost and benefits of potential lifetime gains through citizenship will be undertaken.

Qualitative Assessment

The qualitative research will take the form of a process evaluation building on previous exploratory and preparatory work (22). It will contribute to the assessment of the feasibility and acceptability to service users and providers of a pharmacy-led testing and treatment pathway (including identification of barriers and facilitators and unintended consequences of participation).

Interviews will be conducted with small samples of (i) consenting study participants and (ii) professionals providing the pharmacist led pathway by researchers at University of Dundee.

Qualitative interviews will be conducted with consenting participants and professionals using semi-structured topic guides developed in line with the research aims. Topics will not be explored in a prescriptive manner but as part of an open discussion. This flexible format will enable additional salient topics and insights to emerge. In broad terms, the focus for the different respondent groups will be as follows:

One-to-one interviews with consenting participants (all of whom have engaged with the service) will explore views on issues around the delivery and promotion of the pharmacist-led pathway, their response to the offer and delivery of treatment, and any unintended consequences.

Interviews with professionals will explore issues around implementation of the intervention and the trial elements, identify challenges and ways they have been overcome, and perceived response among participants.
With the interviewee's consent, all interviews and focus group discussions will be recorded as digital audio files, which will then be transcribed in full for thematic analysis. Transcripts will be organized using a thematic framework based on topics specified in the topic guide and emerging themes identified through a process of familiarization with transcript texts.

Patient and Public Involvement

In developing the research question and outcome measures for study, pilot work was undertaken using focus groups of people prescribed OST and their carers', to explore their experiences of using community pharmacies [19]. The priorities and experiences of people prescribed OST were further evaluated through a discrete choice experiment, which was used to aid the design of the pharmacy-led pathway [20]. A process evaluation was employed as part of the development of the DBST intervention in pharmacies, where recipients were asked about their experiences and preferences for testing for hepatitis C [21]. The process evaluation approach was also repeated as part of a feasibility study in which the assessment and treatment of hepatitis C in this group was piloted, to further understand how the intervention would be accommodated by participants [22]. The information gained from this exercise has been fed back to groups of service users attending the local community support and harm reduction centre. Patients have not been involved in the recruitment to this study

DISCUSSION

Liver disease has become a major cause of premature death in the developed world and HCV is a major contributor to this burden [27]. The care of people infected with HCV therapy has undergone a paradigm shift due to the efficacy of direct acting antiviral drugs and the consequent simplification of therapy, with highly effective treatment choices marketed across the world [28]. However, new and more effective pathways of care are urgently required in order to enhance testing and linkage to care and treatment [16]. These novel pathways of care need to be carefully evaluated both for efficacy and cost-effectiveness compared to traditional pathways, as well as for unintended consequences. This pragmatic, cluster-randomised trial can provide strong evidence of the effectiveness of a pharmacist delivered care pathway for HCV eradication therapy in patients receiving OST. A comparison will be undertaken with the current clinical care pathway where patients are referred to a conventional clinic to receive their HCV treatment. Trial design has aimed for high applicability in design decisions [24] and this trial is expected to directly inform the future organisation of care.

Ethics and Dissemination

The study will be conducted in accordance with the principles of good clinical practice (GCP).

In addition to Sponsorship approval, approval was received for this study (15/ES/0086) from East of Scotland Research Ethics Committee 2 on 27 May 2016. Caldicott guardian approval was given on 16 December 2016 to allow NHS Tayside to pass information to the cluster community pharmacies about the HCV test status of patients that they are seeing to provide OST supervision. NHS R&D approvals have been obtained from each health board taking part in the study.

Harms

Regular follow up of the participants will occur daily in the DOT arm during the study treatment period by a pharmacist familiar in the trial methodology. For those participants allocated to the conventional therapy, regular clinical follow up will occur in line with prevailing conventional NHS standard of care. At each visit participants will be monitored for expected Adverse Events (AEs) as per the Summary of Product (SmPC) characteristics for the drug treatments used in this study. This is in line with the current standard of care for the NHS and only AEs outside these criteria will formally be recorded as Adverse Events

Bloods for viral load would be performed as outlined in the Study Schedule, at the pre treatment visit and at 12 weeks post completion of therapy, as per the attached study schedule. Data on testing, referral, initiation of (and adherence to), therapy are routinely collected for the HCV clinical data base and these data will also be utilised.
In addition baseline and end of treatment checking of prescribed and non-prescribed medications and drug use, as documented in the study concomitant medications log, will be carried out to investigate the relationship between any adverse events and drug interactions.

Consenting Participants

Potential participants will be approached by pharmacy staff familiar with the trial methodology and trained in Good Clinical Practice. They will be provided with information on the study verbally and via the Patient Information Sheet (PIS) and be given at least 24 hours to consider participation.
At their return visit for screening they will be interviewed by the study pharmacist and asked to sign an informed consent form, once they are satisfied that they have had adequate explanation from the pharmacist explaining the trial to them.

Confidentiality

The data will be collected by the researcher (treatment delivering pharmacist or nurse) on a paper CRF with subsequent transcription to electronic CRF. Electronic storage will be in an encrypted form on a password protected device. The medical notes will act as source data for past medical history & blood results
All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access to study staff only. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor or its designee. The CI and study staff involved with this study will not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties.

Data Protection

The CI and study staff involved with this study will comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. The CI and study staff will also adhere, if appropriate, to the current version of the NHS Scotland Code of Practice on Protecting Patient Confidentiality. Access to collated participant data will be restricted to the CI and appropriate study staff. Computers used to collate the data will have limited access measures via user names and passwords. Published results will not contain any personal data that could allow identification of individual participants.

Trial Organisation

Trial management

Overall management of the trial is being provided by the Tayside Clinical Trials Unit (TCTU), a UK Clinical Research Collaboration (UKCRC)-registered clinical trials unit. A study Clinical Trial Manager supported by a Study Coordinator will oversee the study and will be accountable to the Chief Investigator (CI). They will be responsible for checking the Case Report Forms for completeness, plausibility and consistency. However, this remains the overall responsibility of the CI. Any queries will be resolved by the CI or delegated member of the study team.

A study-specific Delegation Log will be prepared for the study at each site, detailing the responsibilities of each member of staff working on the study.

A Trial Steering Committee will be established to oversee the conduct and progress of the study. The Steering Committee will include the investigators above, as well as the NHS Tayside Director of Pharmacy and a representative from the Chief Pharmaceutical Officers Team at the Scottish Government. The Steering Committee will take all executive decisions. The responsibility of the Steering Committee is to ensure the scientific integrity and quality of the project. To achieve this, the specific responsibilities of the Steering Committee include: maintaining adherence to the study protocol; approving changes to study protocol if required; reviewing quality assurance indicators; monitoring study recruitment and the overall study timetable; advising, as required, on specific scientific items that may arise; compliance with legislation; adherence to research governance; reporting to funders; approving publication and dissemination strategies. The Steering Committee will meet every 6 months.

Trial Status

Recruitments commenced in December 2016. On 9 October 2017, 234 were consented to the trial.

Reporting guideline: SPIRIT 2013 statement: defining standard protocol items for clinical trials

http://annals.org/aim/article/1556168/spirit-2013-statement-defining-standard-protocol-items-clinical-trials

The references to this paper are located in the manuscript provided in Appendix 9.6

5.3 Clinical effectiveness of pharmacy-led versus conventionally delivered antiviral treatment for Hepatitis C in patients receiving opioid substitution therapy: a pragmatic cluster randomised trial

The following paper is a verbatim copy of Radley A, de Bruin M, Inglis SK, Donnan PT, Hapca A, Barclay ST, Fraser A, Dillon JF (Prepared for submission to The Lancet Gastroenterology and Hepatology February 2020)

SUMMARY

Background: Highly-effective direct acting antiviral drugs (DAAs) provide the opportunity to eliminate Hepatitis C (HCV) infection. This study examined whether a community pharmacy pathway increased HCV testing, treatment uptake and completion, and cure rates for people receiving opioid substitution therapy (OST), compared to conventional care.

Methods: This cluster randomised trial was performed in 55 community pharmacies with patients receiving OST. Pharmacists either referred patients with evidence of HCV antibodies to conventional care (27 pharmacies) or treated them in the pharmacy (28 pharmacies). All pharmacies offered dried blood spot testing (DBST). In the pharmacy arm, infection with HCV genotype 1 or 3 was confirmed, assessment bloods were taken, and DAAs were prescribed by a pharmacist. In the control arm, the patient received care outside the pharmacy. Once prescribed, medication in both arms was delivered as daily modified directly observed therapy alongside OST. The primary outcome was number of sustained viral responses 12 weeks (SVR12) after treatment completion compared to total number of people receiving OST treatment at the participating pharmacies. Trial registration: NCT02706223.

Findings: More OST users in the pharmacy arm versus the conventional care arm agreed to DBST (245 vs 145, OR 2·292, 0·968-5·427, p=0·059); more patients diagnosed with HCV, initiated (112 vs 61, OR 1·889, 1·276-2·789, p=0·0015) and completed treatment (108 vs 58, OR 1·928, 1·321-2·813, p=0·0007); more patients achieved the primary endpoint SVR in the pharmacy arm compared to the conventional arm (98 vs 43, OR 2·375, 1·555-3·628, p< 0·0001).

Interpretation: Transferring the primary responsibility for initiating HCV care to pharmacists, and increasing convenience of HCV testing and treatment initiation for OST users, could be an important strategy in eliminating HCV.

Funding: Partnership between the Scottish Government, Gilead and Bristol Myers-Squib.

INTRODUCTION

Hepatitis C (HCV) is a blood-borne viral infection causing liver disease. The world-wide burden of HCV infection has been estimated as 71·1 million infections (62·5—79·4).[1] In developed countries, people who inject drugs (PWID) are the group most commonly infected with HCV infection and around 10 million or 60% of PWID have been infected worldwide.[2] It has been estimated that 80% of HCV infections are caused by injecting drug use in Western Europe.[3] In current HCV testing and treatment pathways within the United Kingdom, only a small proportion of those who had a positive HCV test had evidence of ever receiving treatment (11·9%) and a smaller number were demonstrated to have achieved a sustained virological response (SVR) (5·9%).[4]

The conventional care pathway in the United Kingdom recommends that patients with a history of intravenous drug use, or those currently prescribed OST, should be offered HCV testing annually. Testing may be available from their GPs, drug workers, drug agencies, social workers, community pharmacies and needle exchanges. Once diagnosed, patients can be referred to established treatment pathways, usually based around hepatology or infectious disease teams in secondary care.[5] The inefficiency of established treatment pathways with many patients lost from care, leads to increased preventable deaths from HCV and viral transmission within the injecting population.[6]

A variety of reasons may explain the low rates of HCV testing, treatment uptake, and treatment completion. At the patient level, PWID may encounter a number of barriers that prevent them from accessing care, including perceptions or experience of stigma and discrimination, issues with the organisation of care and the treatment policies of providers or payers.[7] Low levels of health literacy may also limit understanding of their health, illness and treatments; and PWID may find it difficult to consistently attend medical clinics.[8, 9,] Hence, simplifying care pathways to enable treatment initiation and clinical monitoring, and close treatment supervision in a familiar and convenient setting may be effective in overcoming these barriers.[8] Offering HCV care in primary care and community settings may increase uptake of treatment whilst maintaining high rates of cure.[6]

In the United Kingdom, PWID on OST receive treatment regularly from their local community pharmacy.[10] Patients therefore visit pharmacies much more often than secondary care sites and pharmacies may be located nearer to areas of socio-economic disadvantage, have longer opening hours and can be accessed without an appointment. Pharmacy staff may be trained to offer Dry Blood Spot Testing (DBST) to screen for

HCV infection. Whereas in conventional care, following a positive HCV antibody test, patients are referred onwards to a secondary care site, the opportunity to provide all diagnostic and treatment prescription services from the pharmacy may represent a much more convenient and non-threatening route to HCV treatment for PWID on OST. Moreover, at the pharmacist level, having primary responsibility for HCV testing and treatment; and being able to offer potential HCV patients a more convenient and acceptable treatment pathway, could enhance pharmacists' motivation and effort to recruit patients to the pathway.

The World Health Organisation (WHO) has set targets to eliminate HCV as a public health threat by 2030.[11] Creating the complex public health interventions necessary to eliminate HCV needs well-designed cross-disciplinary programmes put in place to increase screening, testing and diagnosis.[12] Strategies advocated to increase linkage to care include integration with other services, decentralisation to primary care providers and task-shifting to non-specialists.[6]

The current pragmatic, cluster-randomised trial was designed to evaluate whether a pharmacy-led pathway compared with conventional care, increases HCV testing, treatment uptake and completion, and ultimately cure rates for the population of OST recipients infected with HCV.

Evidence before this study

Direct-acting antiviral drugs (DAAs) have a much higher cure rate for HCV than previous medication regimes containing interferon and ribavirin and a much lower treatment burden and monitoring requirement. Consequently, DAAs have mostly replaced these older drugs in current practice and these simple treatments are advocated by the World Health Organisation as a key tool in the elimination of HCV by 2030. Guidance on the prevention, care and treatment of people with HCV recommends task-shifting to optimise available human resources and decentralisation of care to places where people with HCV infection already visit, so that the scale and reach of provision can be increased to achieve elimination. DAAs may be delivered in the community by affiliated care professionals including pharmacists. We undertook a systematic review and meta-analysis of community-based treatment pathways and identified 17 studies demonstrating that locally delivered care is feasible and can deliver increased uptake of treatment. Such clinics may be able to demonstrate similar cure rates to those achieved by specialist clinics in secondary care. However stronger study designs comparing community pathways with

specialist care are needed to give more certainty about the effect size seen in current studies.

Added value of this study

This cluster randomised controlled study demonstrates that pharmacists are more likely to recruit patients to the HCV care pathway, and that patients are more likely to engage with and complete treatment, when the entire process of diagnosis and treatment is offered in the pharmacy. There was no evidence of disadvantageous effects, such as lower treatment completion rates

Implications of all the available evidence

Transferring the primary responsibility for HCV diagnosis and treatment to community pharmacies, is likely to increase HCV uptake and cure rates. It may be that this intervention could play an important role in the test-and-treat approach in order to eradicate HCV. Such services are in line with the WHO guidance for decentralisation of service delivery to primary care-based sites and of task-sharing. Close working between specialist teams and community and primary-care providers may thus offer an effective option for combating HCV in this patient group and moving towards elimination of HCV.

METHODS

Study design and participants

This is a cluster randomised controlled trial comparing HCV care pathways for patients receiving OST in community pharmacies, conducted in 55 community pharmacies in 3 Health Boards. Ethics approval granted by East of Scotland Research Ethics Committee 2 (15/ES/0086), sponsor, research & development and Caldecott approvals by University of Dundee, NHS Tayside, NHS Grampian and NHS Greater Glasgow and Clyde. The protocol, has been published elsewhere. [13].

The unit of randomisation in the trial was the eligible pharmacies. These were community-based, could offer DBST for HCV by trained pharmacy staff and had around 30 or more patients attending to receive OST, to ensure adequate recruitment. Within those pharmacies, all patients on OST were considered to be included in the trial. Those eligible for receiving treatment in the pharmacy care pathway, had to be HCV Polymerase Chain Reaction (PCR) positive, infected with HCV genotype 1 or 3, using OST and willing to have a pharmacist supervise their antiviral drug administration. Patients were ineligible for receiving treatment in the context of this trial if they had a HCV genotype other than 1 or 3, evidence of current or previous decompensated liver disease, Human Immunodeficiency Virus (HIV) infection, surface antigen of Hepatitis B Virus (HBV)

HBsAg positive with detectable HBV DNA, aggressive or violent behaviour towards pharmacy staff, being pregnant, and not being able to provide informed consent.

Randomisation

Prior to the start of recruitment, pharmacies were randomised into conventional care (group 1) or pharmacist-led care (group 2) using http://www.randomization.com (by SKI). Neither pharmacists nor patients were blinded to treatment allocation, as knowledge of the intervention provided was considered to be elementary to entering the pathway, i.e., undergoing HCV testing and initiating HCV treatment.

Procedures

Prior to trial initiation, Good Clinical Practice training was provided to all pharmacies participating in the study. In addition, training was provided on testing for blood borne viruses, the interpretation of laboratory bloods, Fib4 calculation to assess risk of cirrhosis. HCV and its treatment. [14]

Once the trial commenced, pharmacists in the conventional care pathway opportunistically discussed HCV infection with OST patients attending the pharmacy. Those with unknown HCV status or previous negative results could be offered testing using a DBST in the pharmacy. Those recently or previously identified as having HCV were provided with an information leaflet explaining that their pharmacy was participating in a study, asking them to consent to having their data collected. They also received a post-test discussion with the pharmacist using a standard infographic (supplementary file 1) and were offered referral to a treatment centre. When the patient attended an appointment at a treatment centre, a member of the specialist hepatitis team undertook an assessment for treatment for HCV as per standard of care. Assessment comprised of medical history, concurrent medication and assessment bloods including full blood count, urea and electrolytes, liver function testing and viral parameters (genotype and load). Prescriptions for DAA treatment were provided by a nurse prescriber and dispensed at the participant's community pharmacy.

Similar to the conventional pathway, in the pharmacist-led pathway, pharmacists opportunistically discussed HCV infection with OST patients attending the pharmacy, offering DBST testing, and communicating the possibility of receiving DAA treatment to those tested positively (including patients tested positively on a previous occasion, but who had not undergone treatment) in the pharmacy. People identified as being HCV antibody positive consented to receiving their treatment from the pharmacist rather than conventional care, and for their data to be collected. In the pharmacy-led pathway, the

pharmacist assessed the participant for treatment, solely within the pharmacy. They completed a pre-treatment checklist of medical co-morbidities, took a medicines history and identified factors likely to impinge on treatment compliance. A visit from a peripatetic phlebotomist or nurse was arranged in the pharmacy for assessment blood tests and the pharmacist determined suitability for treatment. Where there were no contra-indications to therapy, the patient commenced treatment. In patients where there were identified contraindications or queries about suitability, the pharmacist contacted the specialist hepatitis team for advice. Potential participants with a FIB-4 score of >3.25 were referred to a hospital consultant. Prescriptions for treatment in the pharmacist-led pathway were provided by a pharmacist prescriber or through use of a patient group direction. [15]

The anti HCV treatment provided in both pathways was sofosbuvir/ledipasvir for 8 weeks in genotype 1 infections and sofosbuvir and daclatasvir for 12 weeks in genotype 3 infections. The DAA dose was administered concurrently with supervised OST treatment by the participant's pharmacy, who observed consumption (modified directly observed therapy). In both arms of the study DAA treatment was delivered jointly with OST in their normal pharmacy; although at weekends, patients usually self-administered. For doses that patients self-administered, the pharmacist and patient made a brief if-then action plan (an implementation intention) and coping plan (to overcome anticipated barriers). [16]

Daily monitoring was undertaken at the pharmacy, recording any occurrence of side-effects or adverse events. Participants who did not attend the pharmacy for seven consecutive days had treatment discontinued. Fidelity of the intervention in both arms was promoted through standardised training and concurrent support from the study coordinators. Any breaches of protocol were reported to the Sponsor. A comparison of the pathways is illustrated in Figure 1 and a comparison of patient and pharmacist behaviours illustrated in Figure 2.

Outcomes

The Primary Outcome of the study was the rate of sustained viral response at 12 weeks, (SVR12) in the pharmacist-led pathway compared with that of the conventional pathway 12 weeks after completion of HCV therapy, over the total number of patients on OST in each treatment arm (denominator).

Secondary outcomes assessed key points on treatment pathway, using the care cascade convention. [17] These were comparison of rates of DBST testing between the pathways, DAA treatment initiation, and DAA treatment completion.

Statistical analysis

The primary analysis was undertaken at the individual level using the intention-to-treat principle. Sample size calculations assumed that approximately 3% of HCV positive OST patients enter HCV therapy per year via conventional pathways, with 2.5% of the total eligible population achieving SVR per annum. If it is estimated that the new pathway increased this to 15%, a sample in each arm of 141 (2N=282) will give 90% power at the significance level. The clustered design requires inflation to account for intracluster correlation, so if the average infected subjects per pharmacy are 12, the inflation factor for sizes of cluster, assuming an intra-cluster correlation of 0.05, is 1.55. This leads to a need for 2n=437. The analysis was verified by an independent statistician.

The primary outcome of SVR was assessed as a binary outcome for subjects and utilised logistic regression modelling in STATA. An intention treat analysis was used, so all missing SVRs were assumed treatment failures, thus there was no missing data in the primary outcome. The numerator was the number of subjects achieving SVR at 12 weeks and the denominator was the number attending for OST, since this represents the population at risk of infection and not all patients had been tested. In post hoc analysis an estimated number of infected patients was also used based on national survey data [18]. In order to account for the clustered nature of the trial, a mixed-effects logistic regression model was performed with the parameter indicator of trial arm in the model and a random parameter to account for within-cluster correlation as well as stratified by hub.

For the secondary outcomes on treatment uptake, the numerators were the number of patients who (a) undergo HCV testing, (b) initiate HCV treatment, (c) complete the 8 or12-week HCV course, (d) number of patients with SVR at 12 months (to assess the impact of potential re-infection). Secondary binary outcomes have been analysed using the same procedure, initially as intention to treat with all eligible patients as the denominator and then to explore the steps in the pathway by per protocol. Post hoc analysis was performed to investigate attrition rates at individual steps, where they were similar between the two pathways, to explore any differences in patients' behaviours once they had reached that stage.

Role of the funding source

The funders of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all data in the study and the corresponding author had final responsibility for the decision to submit for publication.

RESULTS

Between 9 December 2016 and 31 May 2018, there were 2718 opioid substitution therapy (OST) recipients attending the 55 study pharmacies (intervention n=28 and control n=27). This total number is used as the denominator for the primary outcome analysis. Detailed information is only available for those who consented to have data collected when they elected for therapy: this was a total of 356. The remaining 2,362 OST recipients would be those; HCV negative, previously treated or who declined testing. To our knowledge no eligible patients were treated outside the trial. All patients previously had the opportunity to access HCV treatment via other pathways prior to the trial. Evidence of HCV infection was required to enter treatment. This was already available for many patients, but the availability of treatment stimulated additional testing.

Treatment effects along the pathway: from diagnosis to cure

With regard to the uptake of HCV testing in the treatment arms (secondary outcome), we observed that 245 DBST (77 antibody positive) were conducted in the pharmacist-led arm and 145 (31 antibody positive) in the conventional pathway (Odds Ratio 2·292, 0·968-5·427). In total, 356 (137 in the conventional care pathway and 219 in the pharmacy-led pathway) newly diagnosed patients, and previously diagnosed patients who did not opt for treatment in the pre-DAA era, consented to receiving DAA treatment after being approached by their pharmacists (OR 1·696, 1·350-2·131, p<0·0001). Sixty-one participants consecutively initiated treatment in the conventional care arm and 112 initiated treatment in the pharmacist-led pathway (secondary outcome, OR 1·889, 1·276-2·789, p=0·0015). Treatment initiation rates amongst those consenting to treatment was very similar in both treatment arms (61/137 (44·5%) for the conventional and 112/219 (51·1%) for the pharmacy arm.

A total of 58 and 108 participants completed treatment in the conventional and pharmacy arm, respectively (OR 1·928, 1·321-2·813, p=0·0007). Treatment completion rates amongst those who initiated treatment, where again very similar between treatment arms 58/61 (95·0%) for the conventional and 108/112 (96·4%) for the pharmacy arm.

Forty-three participants demonstrated SVR12 in the conventional care arm compared to 98 in the pharmacist-led arm (OR 2·375, 1·555-3·628, p<0·0001) (Table 1, Figure 3). There were two treatment failures in each arm. Of the treatment completers, twelve participants did not attend for an SVR12 test in the conventional care arm and six participants did not attend for an SVR test in the pharmacy-led arm (two patients died from unrelated causes). One participant in the conventional arm and two participants in the pharmacy-led arm attended for an SVR12 test, but had an insufficient sample taken to complete the PCR test.

One participant in the pharmacy-led arm withdrew after assessment before initiating therapy because of pregnancy. One pharmacy-led participant was discontinued from treatment due to missing seven consecutive days of therapy. Five participants dropped out during treatment (3 conventional care arm, two pharmacy led arm) through personal choice. During the study no serious adverse events (SAEs) were identified.

We would assume that patients completing treatment, but not achieving a confirmatory test would also have attained an SVR, given the high cure rates amongst treatment completers and the provision of directly observed therapy as part of the intervention. There were larger numbers of participants not attending for a confirmatory test in the conventional arm.

Additional participant characteristics

Detailed patient information was collected for those who consented to have additional data collected, which was asked when HCV positive OST users elected to initiate HCV therapy (n=356). The remaining 2,362 OST recipients were HCV negative previously treated or who declined testing. Assessed characteristics of the consented cohorts were similar between groups of pharmacies (Table 2) and participants except for genotype, where the pharmacy-led arm had more genotype 3 patients (Table 3). Data on recruitment, testing, initiation and completion of treatment and gaining of an SVR 12 by site is shown in Table 4.

DISCUSSION

This study presents evidence that pharmacies can provide a clinically effective pathway for testing and treatment of HCV, as demonstrated by an adequately powered cluster randomised controlled trial. In a population that had been exposed to multiple testing and treating opportunities over a number of years, with a high proportion of the HCV infected population already treated [19], the pharmacist-led pathway brought more people on OST into HCV treatment. This was achieved through both diagnosing patients who had

previously never been tested, as well as initiating therapy in the newly diagnosed and those previously diagnosed who had not been initiated into treatment.

Our intervention development work demonstrated that being treated with respect was of prime importance to recipients of care, and that experience of stigma and discrimination in healthcare systems was widespread. [20, 21] At each point in the care pathway, the pharmacist-led pathway provided advantages in terms of the retention in care. Using community pharmacies as the focal point of this intervention enabled a number of the identified barriers to care to be overcome. Their local nature and the longitudinal trusting relationships formed between the pharmacies and people attending for OST was an important factor in encouraging engagement. These established relationships may have overcome perceived and real barriers to care, caused by the stigma and discrimination experienced by the group. The on-site delivery of the intervention also enabled participants experiencing poverty and with low health literacy to engage in care. The familiarity of the local community setting may have increased willingness to engage in the intervention with fewer barriers preventing attendance: less difficulty in managing to attend and finding money to travel [8, 9], and fewer problems with navigating the health system. [22] Evidence from the feasibility trial confirmed that a significant loss to follow-up occurred when participants were asked to attend for phlebotomy outside of the local pharmacy. [23] Since the pharmacist-led intervention was based around the delivery of OST, participants had a strong incentive to attend.

The cure rates achieved in the pharmacy-led arm for both the diagnosed population (45%) and notional population of infected individuals (18%) compare favourably with the outcomes reported for other pathways (12%, 6%). [4, 24] The conventional care arm in this study is described as standard of care, which it is in Scotland. However, this pathway represents a gold standard pathway of care for HCV infected OST patients compared to conventional secondary care based models.

Testing for HCV was not part of the trial and was already routinely available in some pharmacies before the study; all pharmacies had to develop a testing service to participate. The study clearly reached people who had not been previously engaged in HCV care, despite other testing opportunities being available, as recommended in all guidelines and by all health services they interact with. The observed increased uptake of treatment may reflect the convenient co-location of testing and OST pickup to the patient, but equally may be due to the financial incentivisation of the pharmacist by the item of service mechanism established in the United Kingdom National Health Service. In the

study treatment pathway there were two very noticeable drop-offs in the cascade of care: initial consent to participation and initiation onto treatment; thereafter there was with little drop off to cure. At the point of considering treatment, both the patient and the pharmacist know whether further care in the pharmacy or referral to another site and other health care professionals is available. The pharmacist led pathway was significantly more likely to lead to treatment initiation. The reasons behind this could be pharmacist related: they are more motivated to recruit as they would be having a new therapeutic experience and will also be financially rewarded. The patient related factors may include: ease of treatment without having to travel elsewhere; removing the fear of stigma and unknown situations. The second drop off in the cascade of care is at initiation of treatment. In the pharmacist-led arm, this means that blood tests have been taken, but in the conventional arm, this means that the participant must have travelled elsewhere to meet with a nurse. A greater drop off at this point is again observed in the conventional care arm despite this already being a more selected population. This emphasises the barrier that venepuncture still raises in the cascade of care, as this skill set is not widely available in many addictions settings; whilst many virology tests can now be done on fresh or dried capillary blood, the remainder need to be performed on whole blood or plasma. The safety of DAAs should mean that many of the routine analytes measured are no longer required. The only outstanding issue is fibrosis estimation which cannot be performed on capillary blood but can be managed with imaging modalities such as elastography.

The study had a number of strengths. The intervention was developed iteratively and pragmatically using the Medical Research Council Guidance for developing and evaluating complex interventions. [25] Pilot work was undertaken using focus groups of people prescribed OST and the priorities and experiences further evaluated to aid the design of the pharmacist-led pathway [20, 21] A process evaluation was employed as part of the implementation of the DBST intervention in pharmacies and this was repeated in a feasibility trial. [23]

For pharmacy staff, the intervention was viewed as straightforward to deliver and integrated with an established activity. [23] Dried blood spot testing was within the competency of staff and provided advantages to participants who were reticent to allow venous access. [26] A peripatetic phlebotomist was often able to work closely with pharmacy staff and meet with patients; the use of DAAs meant that monitoring and management were straightforward; assessment of risk of cirrhosis could be achieved using blood tests; on-going monitoring of participants was undertaken during routine

attendance for OST. The failure to gain assessment bloods was the main reason for loss of participants after consenting before initiation, as this was the only step they had to perform. The recent introduction of pangenotypic treatments reduces the complexity of evaluation, with an assessment for fibrosis being the main requirement and further reduces the need for monitoring carried out in this study. [27]

Pharmacies lack access to a range of information sources that may be available to hospital clinics, meaning that a detailed medical history with evidence of health care interactions were not available to pharmacy staff. This proved not to be a barrier to care. Close working with the specialist hepatitis team meant that any queries raised by the pharmacies could be efficiently dealt with through e-mail or phone. These queries were considered during a weekly multi-disciplinary team meeting. Pharmacies had good knowledge of concurrent medication.

In Tayside, where pharmacies had been involved in testing and treating hepatitis C since 2013, involvement in this study was unsurprising. In Glasgow and Grampian, where pharmacies had been less involved in these processes, the invitation to participate was more novel. The participants recruited from the Glasgow site were mainly individuals who had previously tested antibody positive but had not engaged with a treatment pathway. The proportion of participants recruited to the study from these sites was found to be less than for the Tayside sites.

A recent systematic review has evaluated the performance of care pathways that utilise DAAs in a range of community and primary care settings. [28] The WHO Guidelines on care and treatment of persons diagnosed with chronic HCV infection promote simplified service delivery models; integration with other services; decentralised services supported by task-sharing and community engagement to address stigma and increase reach. [6]The studies considered in the systematic review and meta-analysis identified a variety of locations and providers have been used to deliver care to this group of patients. These have included primary care; integrated health care systems; places where people who inject drugs (PWID) are treated; in pharmacies; and through telemedicine. These care pathways have been developed in acknowledgement of the need to provide local services with reach into the communities where people with hepatitis C live. The studies reported positive outcomes for uptake of treatment; completion of treatment; attainment of SVR. As with this study, other evaluators have noted reduced SVR12 rates because of loss to follow-up of patients in community settings. With DAAs SVR rates of greater than 97%

are delivered if patients adhere to treatment, therefore completion of therapy can be a surrogate for SVR. [29]

Other systematic reviews have considered barriers and facilitators to care, as well as the views and experiences of people who inject drugs. [30, 31] These studies concluded that the target groups for HCV often had poor levels of knowledge about the infection and of the processes involved with testing and treatment. A fear of stigma and discrimination and a reticence to discuss risk behaviours tended to prevent engagement. These barriers could be addressed through educating participants and integrating HCV treatment pathways into other services where the target group were likely to go.

This study demonstrates the advantages of developing novel care pathways targeting populations with high prevalence of HCV. Provision of HCV treatment in familiar surroundings with the additional benefit of directly observed treatment arrangement, may increase attainment of SVR. Achievement of these factors within local health systems needs to be commonplace if the WHO target for elimination is to be met.

Reporting Guideline: Consort extension for cluster randomised trials.

Figure 1: Trial Profile

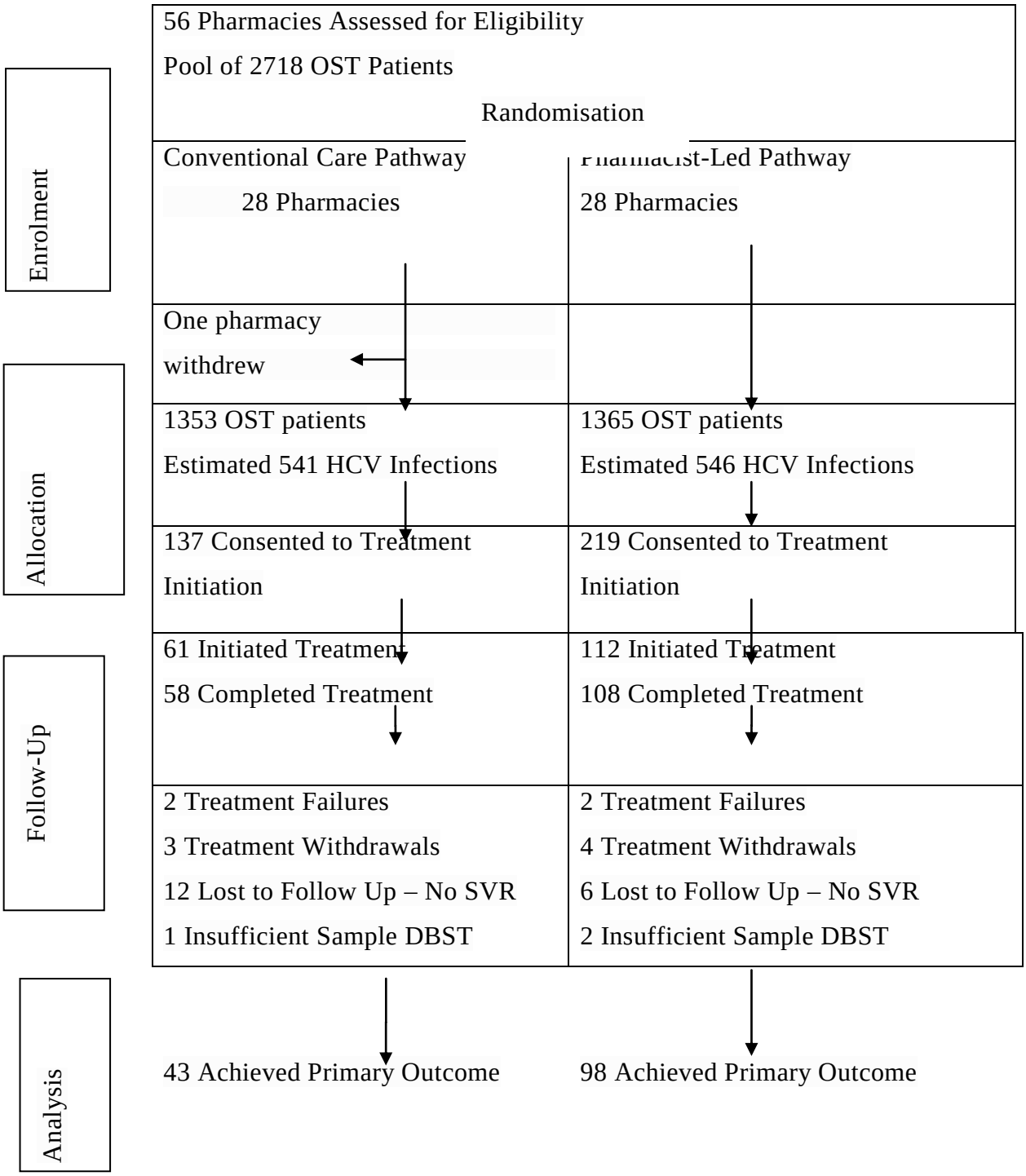


Figure 2: Comparison of patient and pharmacist behaviours in the conventional care and pharmacist-led pathways

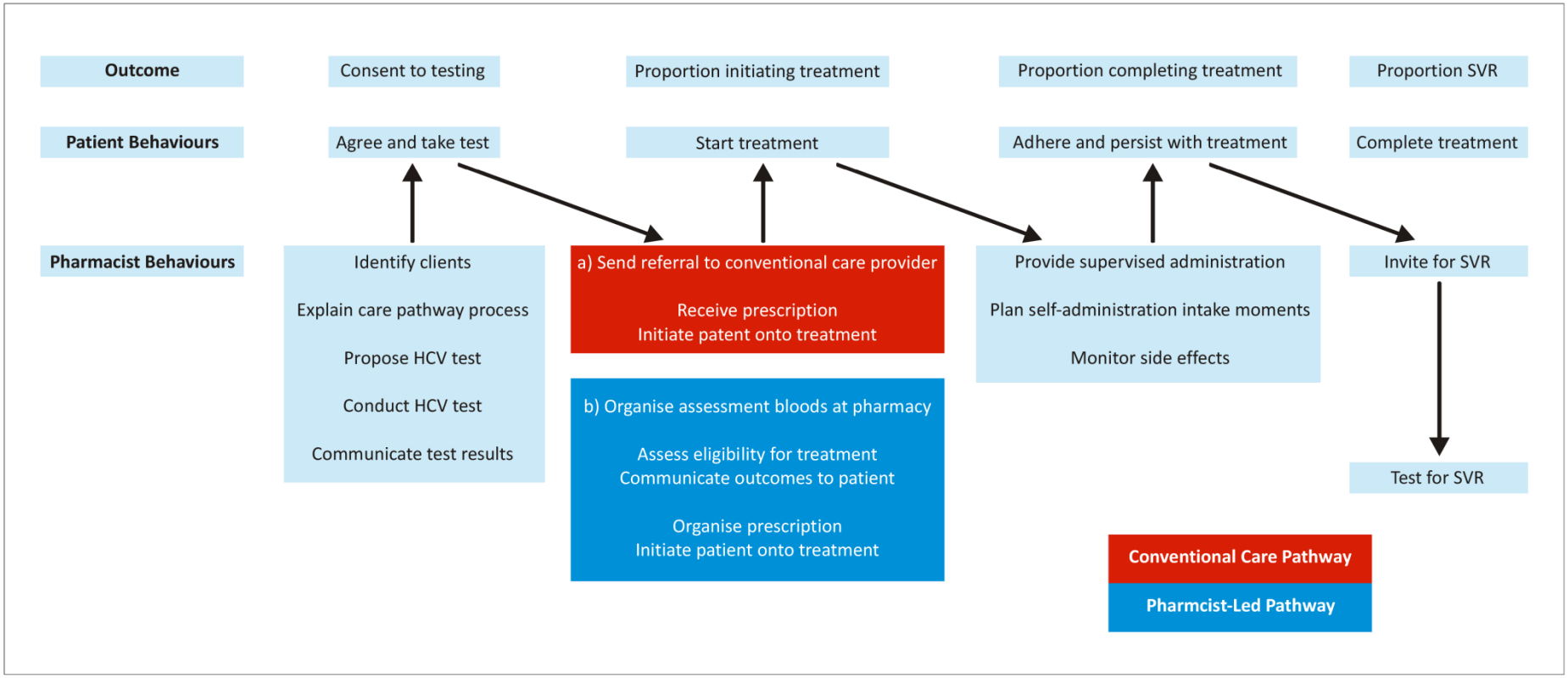


Table 1: Trial Outcomes

Pool of 2718 OST Patients		Odds Ratio	Confidence Limit for Odds Ratio		P value
			Lower	Upper	
Conventional Care Pathway 1353 OST patients	Pharmacist-Led Pathway 1365 OST patients				
43 SVR 12	98 SVR 12	2.375	1.555	3.628	<0.0001
145 DBST taken	245 DBST taken	2.292	0.968	5.427	0.059
137 Consented Participants	219 Consented Participants	1.696	1.350	2.131	<0.0001
61 Initiated Treatment	112 Initiated Treatment	1.889	1.276	2.798	0.0015
58 Completed Treatment	108 Completed Treatment	1.928	1.321	2.813	0.0007
Diagnosed Population Cure Rate*					
31%	45%				
Notional Population Cure Rate+					
8%	18%				

*Diagnosed Population Cure Rate is number achieving primary outcome (SVR12) compared to number of consented participants

+Notional Population Cure Rate is number achieving primary outcome (SVR12) compared to total number of potential participant

Figure 3: SuperDOT-Cascade of Care – Attrition from original cohort to SVR12

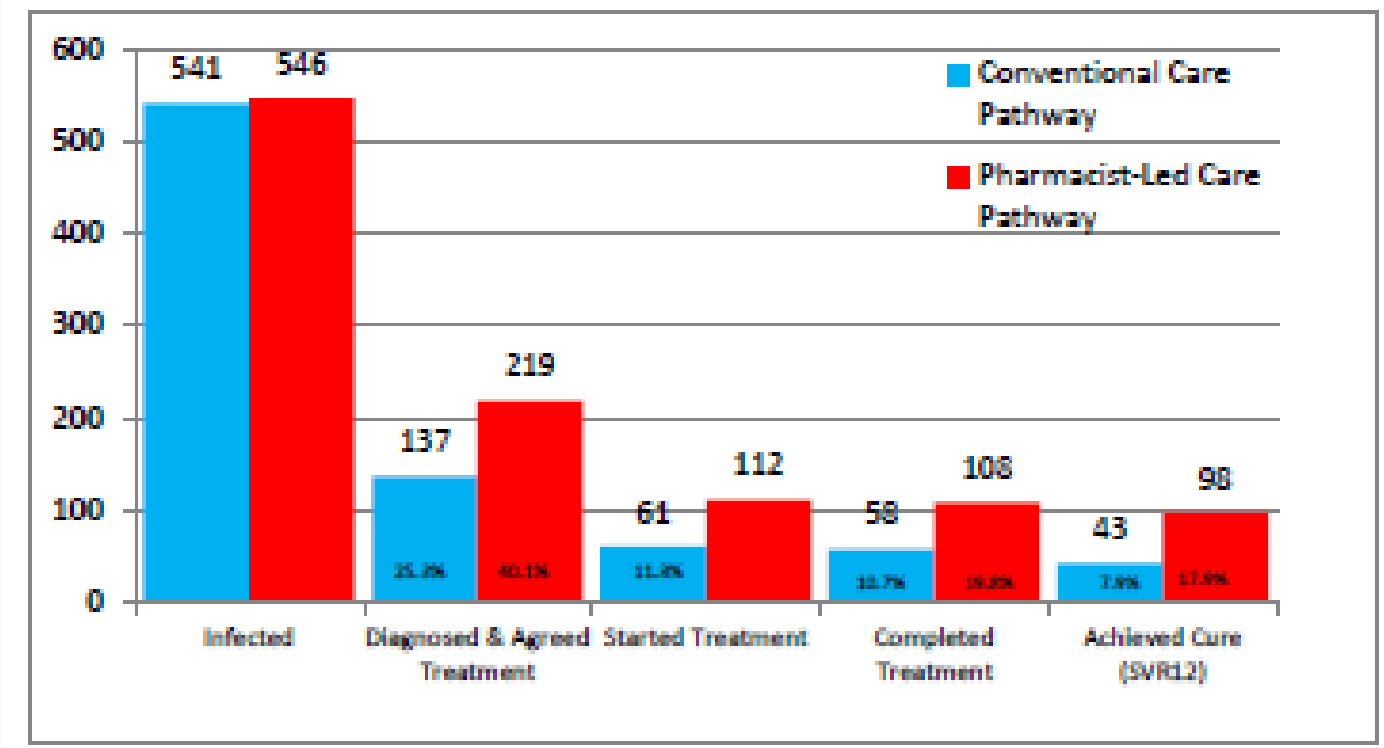


Table 2: Characteristics of Study Pharmacies

Characteristics of the Study Pharmacies	Conventional Care Arm (%)	Pharmacy-Led Arm (%)
Number of OST patients at start of study	N=27	N=28
20-29	4 (15)	3 (11)
30-39	6 (22)	13 (46)
40-49	7 (26)	2 (7)
50-59	6 (22)	2 (7)
60+	4 (15)	8 (29)
SIMD Quintile Pharmacy Address		
1 (most deprived)	17 (63)	14 (50)
2	8 (30)	7 (25)
3	1 (3.5)	4 (14)
4	1 (3.5)	1 (4)
5 (least deprived)		2 (7)

Table 3: Characteristics of consented participants

Treated Study Participants		N=61	N=112
Age Distribution (years)	20-29	3 (5)	3 (3)
	30-39	28 (46)	63 (56)
	40-49	24 (39)	43 (38)
	50-59	4 (6)	3 (3)
	60+	2 (3)	
Gender	Male	43 (70)	70 (63)
	Female	18 (29)	42 (37)
Fib-4	< 1.45	46 (75)	68 (61)
	1.46-3.24	14 (23)	42 (37)
	3.25	0	2 (2)
Genotype	1	30 (49)	37 (33)
	3	31 (51)	75 (70)

Table 4: Recruitment of participants between sites

	Total	Tayside	Grampian	Glasgow
Recruited	356	250	80	26
Initiated Treatment	173	137	21	15
Completed Treatment	166	132	20	14
Drop out during Treatment	7	5	1	1
Drop out before Treatment	2	0	1	1
Achieved SVR	141	113	16	12
No SVR	4	4	0	0
Lost To Follow Up	18	12	4	2
Patient completed DBS error	3	3	0	0

Supplementary File 1

Hepatitis C Testing And Treatment Pathway

- Dry Blood Spot Testing is simple & easy to do
- DBST finds out whether you have been exposed to HCV
- Most people catch HCV by injecting
- Some people rid themselves of the virus (1 in 3)
- Most people need tablets to cure themselves

- A reactive DBST means you may still be infected
- We can tell if you are still infected and need treatment by taking a blood test. The test results arrive quickly
- The results will remain confidential
- Getting a blood test means you can get the treatment you need

- Curing HCV means 1 or 2 tablets a day
- The treatment might last 8 or 12 weeks
- You get the tablets at the chemist each day
- Almost all people are cured by the tablets
- They have very few side effects. These are minor
- The tablets must be taken every day

- Curing HCV is a great achievement
- It will improve the way you feel
- Getting cured is straightforward nowadays
- You can get cured just by following this pathway and attending the pharmacy each day

5.5 Critical Reflection

The cluster randomised trials comprising the content of this chapter were undertaken as the final section of work to model, establish and evaluate an intervention for testing and treatment in community pharmacy. The feasibility pilot was the first opportunity to put all of the elements together: operationalising a research protocol; identifying potential sites and partners for delivering the study; designing trial documentation; designing and delivering training for staff at research sites; putting together site research files; facilitating and supporting research sites to engage and participate fully.

The learning gained from the development and modelling work informed the decisions made when creating the research protocol. This work had ensured an appreciation of the importance of supportive relationships between the client and pharmacy and that the pharmacies should not be applying policies that singled out clients for different treatment. The process evaluation work had provided a number of additional themes to recognise, including an emphasis on confidentiality and the need to locate as much of the intervention pathway as possible in the local community, if not in the pharmacy itself. The waterfall plot (Figure 1) in the paper clearly shows the attrition of participants when they are asked to attend for an appointment at a different site.

From a site operational perspective, the learning had been that a pharmacy team delivered the intervention more effectively than when a single person undertook the study. For this reason, we offered training to teams rather than individuals and offered multiple training days, to encourage as many people as possible to attend. The pharmacy site staff required training in Good Clinical Practice, to ensure good research governance. The study days incorporated a series of theoretical and practical sessions to apply knowledge and develop clinical skills, since many of the training participants had not previously take blood samples for blood borne virus testing and had not interpreted laboratory tests.

The main obstacle to initiating the study was the need to obtain a contract agreement with the pharmacy companies, who each had different approval procedures and governance requirements to be met. Meetings these requirements meant that delays of several months were experienced before the study could be commenced.

The multicentre study “SuperDOT-C” scaled up work considerably, with the need to support and coordinate sites across different areas in Tayside and Grampian and Glasgow Health Board. The different Health Boards in particular, had different administrative arrangements and systems for the same activities. For example, each health board had a

different governance requirement to authorise staff to undertake dried blood spot testing. Therefore the procedures adopted in Tayside had to be adapted when working in the different boards. These differences meant that training and approaches to implementation had to be adapted for the different Boards, to enable that the study could run efficiently. Monitoring and facilitating study progress was much more complicated and challenging and creating productive relationships and lines of communication required lots of work. The involvement of Tayside pharmacies in blood borne virus testing and treatment had been on-going since the research programme was initiated in 2013 and therefore the work was familiar to pharmacy teams. The involvement in blood borne virus testing and treatment was far less familiar to teams from other boards and this presented a further issue to address. This was reflected in the activity and recruitment generated. A lower recruitment was observed for both Glasgow and Grampian sites.

5.5.1 Critique of methods

The methods used in the cluster randomised controlled trials reported in this chapter are the same as those discussed in chapter two and will not be repeated here. For these studies, it was identified that a cluster design was advantageous for a series of reasons. A cluster design meant that there was no requirement for research-naive pharmacy staff to offer more than one intervention in the pharmacy, as they would do if a standard randomised controlled trial design was employed. It was also realised that the client group would soon identify the differences between the pharmacy-led and conventional treatment pathways and the increased convenience of the pharmacy-led pathway might create additional issues. No contamination issues were in fact identified during the course of either study.

In the quasi-experimental study, a difference between the ages of the cohorts was observed for intervention and control groups (chapter4). Within the feasibility study, statistical testing of the ages of both intervention and control cohorts demonstrated that there was no significant difference. This observation therefore provides some evidence of the effect of randomisation in minimising systematic bias.

In cluster randomised trials, statistical power is reduced in comparison to similarly sized conventional randomised designs. Sample size calculations are therefore inflated using a cluster inflation factor to accommodate for the clustering. Within the multi-centre study, there were more than sufficient potential participants within each intervention arm to provide then required power for the study. Work undertaken as part of the systematic

review study (chapter 3) and earlier development work identified the scale of attrition that might be expected to occur in the experimental studies.

The pilot study reports on the simplified structure of the pathways and attributes costs to those pathways, as a first step towards an economic analysis. This baseline work was completed in order to lay the foundations for the full economic analysis and modelling which will be undertaken at the University of Bristol for SuperDOT-C.

The process evaluation for both studies in this chapter, utilised the same methodology, with semi-structured interviews providing data for integration with previous evaluation work, to incrementally increase knowledge of the performance of the intervention. The process evaluation for SuperDOT-C reflected the need to consider different levels of activity and performance between pharmacy sites and differences between Boards, using purposive sampling. This analysis concentrated on an evaluation of staff involvement. The range of views and perceptions described were coherent with the previous work, but also identified some additional perspectives arising from differences in organisational cultures and familiarity with extended professional roles.

5.5.2 Critique of analysis

In the feasibility pilot, the small numbers of participants completing the pathway meant that logistic regression modelling was not attempted and a simple analysis using π^2 testing and estimation of p-values was considered to be sufficient for a pragmatic analysis.

Within the pilot study, a significant imbalance between the two arms was identified by the analysis, with a greater number of participants in the pharmacy arm experiencing spontaneous clearance of their viraemia and a greater number of participants being diagnosed with genotype 3 hepatitis C: the direct-acting antiviral drugs to treat genotype 3 without addition of the rifampicin were not available at the time of the study, although they were available by the time SuperDOT-C was implemented. This imbalance was not prevented by randomisation of pharmacy sites to either intervention or control arms, and may be a feature of the small number of study sites.

In the analysis of cluster randomised trials, failure to control for the correlation between individuals in the same cluster can lead to bias, over-estimating the treatment effect and increasing the chances of type one error; rejection of the null hypothesis (Hahn, Puffer et al 2005). For this reason, a logistic regression modelling was adopted for the analysis of SuperDOT-C, under the supervision of Professor Donnan. The analysis of SuperDOT-C required analysis at three levels (board, pharmacy site, individual), with programming undertaken using STATA to operationalise the statistical analysis plan. The analysis

demonstrated strong evidence that a statistically significant difference could be identified between the conventional and pharmacy pathways that were evaluated by the study.

CHAPTER 6:

MAPPING OF CAUSAL INFERENCES IDENTIFIED DURING THE DEVELOPMENT AND EVALUATION OF A COMPLEX PUBLIC HEALTH INTERVENTION

Content

Using a systems-thinking approach to elucidate programme theory underpinning the effectiveness of the SuperDOT-C Intervention: a pharmacy-led test and treat pathway for PWID with hepatitis c infection prescribed opioid substitution therapy. Manuscript prepared for submission to the International Journal of Drug Policy, July 2019.
Radley A, Inglis SK, de Bruin M, Dillon JF was conceived by Radley and Inglis. Radley and Inglis jointly undertook the thematic analysis and interpretation. Radley, Inglis, de Bruin and Dillon provided methodological and clinical advice. The paper and subsequent drafts were written by Radley with contributions by all co-authors.

Evidence Contributions

This paper reports the analysis undertaken on the experimental and process evaluation work under taken during this programme of study, in order to identify the "active ingredients" of the intervention. Review of literature, research findings and qualitative themes from the programme have been utilised to identify key elements that are thought to influence the SuperDOT-C intervention. These elements are defined as patient behaviour, patient environment, health worker performance and healthcare environment. The elements therefore span individual, organisational and contextual parameters.

Knowledge Translation Contributions

This work has been presented at local and international conferences through both poster and oral presentations. Radley has provided guidance to groups in both the USA and Canada involved in the implementation of pharmacy-based models to test and treat hepatitis C.

6.1 Using a systems-thinking approach to elucidate programme theory underpinning the effectiveness of the SuperDOT-C Intervention: a pharmacy-led test and treat pathway for PWID with hepatitis c infection prescribed opioid substitution therapy

The following paper is a verbatim copy of Radley A, Inglis SK, de Bruin M and Dillon JF prepared for submission to the International Journal of Drug Policy in July 2019

ABSTRACT

Background: Increasing access and linkage to care for hepatitis C (HCV) are fundamental requirements for achieving the WHO target of elimination by 2030. The SuperDOT-C research programme designed and evaluated an HCV test and treat pathway delivered with direct-acting antivirals, through community pharmacists. As part of the process evaluation of the intervention, causal loop diagramming (CLD) was used as a tool to help understand complexity and generate hypotheses about causal mechanisms.

Methods: A systematic literature review and series of community-based participatory research activities were undertaken to inform the design and understand the acceptability of the SuperDOT-C intervention. Qualitative work included implementation of seven focus groups with service users and carers (41 participants), discrete choice experiment with service users (103 participants), semi-structured interviews on service acceptability with service users (14 participants) and staff providers (36 participants). All transcripts were thematically analysed.

A causal loop diagram was constructed with contributors defined as: health worker performance; health care environment; patient behaviors and attitudes; patient environment. Components were identified then assigned polarity and arranged into feedback loops associated with the contributors, with reinforcing (R) and balancing (B) effects. The resultant CLD was used to examine leverage points and the dynamic relationships between them.

Results: 34 components were identified from the literature review and qualitative work and plotted onto a CLD. The CLD was reviewed and 5 reinforcing loops and 2 balancing loops determined. The reinforcing loops described positive patient relationships, proximity to the community and role enhancement as factors promoting uptake of the care pathway. The balancing loops described factors such as experience of stigma and fear of treatment side-effects, but also the factors such as homelessness, healthcare policy and budgetary restraints.

Conclusion: A systems-thinking approach using CLD is helpful in the evaluation of complex public health interventions and forming hypotheses about causal mechanisms.

1.0 INTRODUCTION

Hepatitis C (HCV) is a blood-borne viral infection causing liver disease. The world-wide burden of HCV virus infection has been estimated as 71.1 million infections (62.5—79.4) (The Polaris HCV Collaborators 2017). In developed countries, people who inject drugs (PWID) are the group most commonly infected with hepatitis C (HCV) infection and it has been estimated that around 10 million or 60% of PWID have been infected by HCV worldwide (Gountas, Sypsa, Anagnostou, Martin, Vickerman, ... Hatzakis 2017). The conventional care pathway in the United Kingdom recommends that patients with a history of intravenous drug use, or those currently prescribed OST, should be offered HCV testing annually. In current HCV testing and treatment pathways within the United Kingdom, only a small proportion of those who had a positive HCV test had evidence of treatment (11.9%) and a smaller number were demonstrated to have achieved a sustained virological response (SVR) (5.9%) (Simmons, Ireland, Irving, Hickman, Sabin.... Mandal 2018).

The World Health Organisation (WHO) has set an ambitious goal to eliminate HCV as a public health threat by 2030 (WHO 2016.). Creating the complex public health interventions necessary to eradicate HCV requires that well-designed cross-disciplinary programmes are put in place using different strategies to increase screening, testing and diagnosis (Wade, Veronese, Hellard and Doyle 2016). Strategies advocated to increase linkage to care include integration with other services, decentralisation to primary care providers and task-shifting to non-specialists. In the United Kingdom, opioid substitution therapy is commonly provided by community pharmacies (Matheson, Thiruvothiyur, Robertson and Bond 2016). Hence a more central role in the treatment of HCV for community pharmacists, who are seeing these clients on a regular basis, may lead to increased population coverage through higher HCV testing, treatment uptake, adherence, and treatment completion rates (Mathieson et al 2016).

Evaluations of clinical interventions are often described as linear logical progressions, rather than the non-linear iterative attainment of increasing understanding about how an intervention performs within a particular context (Craig, Dieppe, Macintyre, Michie, Nazareth and Petticrew 2008). A variety of methodological approaches have been proposed as ways to conceptualise an understanding of the processes involved that determine the effectiveness of an intervention. These processes have included the

application of change theory (Rogers 2008), the use of a realist evaluation approach (Pawson and Tilley 2015), theory-driven evaluation (Renmans, Holvoet and Criel 2015), and systems thinking (Best, Berland, Herbert, Bitz, van Dijk ...and Millar 2016). A systems thinking approach can be a useful way of considering the nature of the complex adaptive systems seen in health services. Such an approach takes a wider perspective, considering interaction effects, feedback loops and emergence within the larger system (Carey, Malbon, Carey, Joyce, Crammond, Carey 2015). Causal loop diagramming is a tool used to analyse complex systems. It is a qualitative visual aid used to communicate assumptions about a dynamic system (Belue, Carmack, Myers, Weinreb-Welch and Lengerich 2012). Visualizing complex adaptive systems can enable a better understanding of the behaviour of the system and its agents. A specific function of the tool is to elucidate feedback loops (Cavana and Mares 2004). Use of such visualizations can be used to generate hypotheses which feed into theory-driven evaluation and exploration of potential causal mechanisms and routes to improvement (Renmans et al 2015).

In undertaking a programme of research to develop, implement and evaluate a pharmacist-led testing and treatment pathway, we undertook a series of exploratory and feasibility studies (Radley, de Bruin, Inglis, Donnan 2018). This study is part of the DOT-C research programme evaluating the implementation of a pharmacist-led test and treat programme for hepatitis C in people prescribed opioid substitution therapy.

2.0 MATERIALS AND METHODS

2.1 Study Setting

In 2016, an estimated 34,500 individuals were living with chronic HCV infection in Scotland, more than half of whom have been diagnosed (Health Protection Scotland and Glasgow Caledonian University 2017). Of those aware of their infection, around a quarter engaged in specialist treatment and approximately 1750 cases were treated per year. Injecting drug use continues to be the most prominent risk factor for HCV infection in Scotland, accounting for over 90% of infections. In 2015-16, results from the Needle Exchange Surveillance Initiative (NESI) showed that HCV antibody prevalence among people who inject drugs (PWID) remained high at 58% (The Needle Exchange Surveillance Initiative 2017) there were no major differences in HCV prevalence by gender or age-group over time, with rates in the younger (≤30 years) and older (>35 years) age-groups stable at around 40% and 65%, respectively.

The policy context set by the Scottish Government is described in the Sexual Health and Blood Borne Virus Framework 2015-2020 Update (Scottish Government 2015). This

document sets out targets for Scotland, aiming to treat at least 1,500 people per year with antiviral therapy and aiming for a 75% reduction in the annual number of people developing hepatitis C-related liver failure and/or liver cancer by 2020.

The Tayside region of Scotland has been a test bed for sequential development of integrated services over the last two decades (Tait, Wang, Stephens, Miller, McIntyre... and Dillon 2017), moving from standard secondary care-based hospital outpatients, onto nurse-supported treatment services, then to a HCV managed care network (MCN)(Tait, McIntyre, McLeod, Nathwani and Dillon 2010; Jafferbhoy, Miller, Dunbar, Tait, McLeod and Dillon 2012) and finally to a development in the MCN model which included a widespread dry blood spot testing programme in drug services and development in our outreach services across the region which included providing treatment within drug services and prisons (Tait, Stephens, McIntyre, Evans and Dillon 2013)

2.2 Data collection and Analysis

A systematic literature review (Radley, Robinson, Aspinall, Angus, Tan and Dillon 2019) and series of community-based participatory research activities were undertaken to inform the design, development and implementation of the SuperDOT-C intervention. Qualitative work included implementation of a focus group series with service users and carers (41 participants (Radley, Melville, Easton, Williams and Dillon 2016), a discrete choice experiment (DCE) with service users (103 participants) (Radley, van der Pol and Dillon 2019), semi-structured interviews on service acceptability with service users (14 participants) and staff providers (36 participants) (Radley, Tait and Dillon 2018)

Focus Group Series

Seven focus groups with a total of 41 participants were undertaken during 2015 in a range of settings, aiming to gain a diversity of views and experiences. Participants were people prescribed OST by the specialist substance misuse service in Tayside, who provide the majority of care for this group. Participants discussed comparative experiences of partners, family and associates who had undertaken testing and treatment for HCV.

Recruitment to the focus groups utilised the following variables:

-Place of Residence –large urban / other urban / accessible small town

-Service Users detained by the Criminal Justice System

-Perspectives of peer mentors (service users at an advanced stage of recovery)

Sessions were open-ended and ranged from 70–100 minutes. A discussion guide was developed from a literature review and discussion with the research team. The first focus

group served as an internal pilot to test the discussion guide. The seventh focus group with peer mentors was undertaken to provide perspective on the findings from this study. In the local service configuration, peer mentors are experienced service users who have received OST for a number of years and are further along a recovery pathway: we listened to their reflections and perspectives on the themes that had emerged.

Data from each focus group were digitally recorded and transcribed verbatim, before being coded and analysed by two researchers. Analysis drew on the constant comparison method, which was operationalised within a general thematic approach (Ritchie and Spencer 1994).

Discrete Choice Experiment

Focus group participants described a range of attributes that had significant overlap with those identified from the literature: stigma, waiting times, confidentiality of results and positive relationships with service providers. The final attribute list included the pre-determined attributes (who does the testing (provider) and incentive payment) as well as the most important attributes identified through the literature review and focus groups (whether treated with dignity and respect; travel distance; and waiting time to test result). The five attributes were utilised in a discrete choice experiment which aimed to elicit OST user's preferences for HCV testing, in order to aid the design of a testing service that was acceptable to use from their perspective. Plausible levels were assigned to each attribute based on focus group responses and the local context for factors such as laboratory turnaround and travel distance. The attributes and levels in the DCE were selected following recommended practice (Reed Johnson, Lancsar, Marshall, Kilambi, Mühlbacher...and Bridges 2013).

A questionnaire in three sections was administered to 103 consented participants. The sections ascertained participants' preferences on the levels within the chosen attributes; presented the 16 choice sets and collected details of patient demography including age, sex, educational level and employment. Respondents completed the questionnaire in the presence of one of the researchers who provided support where required. The administration of the questionnaire in a familiar environment was also chosen, to reduce participant stress and enable access.

Semi-Structured Interviews

Interviews were held with 14 participants who had either tested HCV antibody positive, or had participated in the pharmacy-led pathway. Interviews were conducted using topic guides developed in line with the research aims and programme theory. All interviews

were recorded as digital audio files and transcribed in full for thematic analysis. Transcripts were inductively analysed to identify themes emergent from the interviews. These data contributed to the assessment of feasibility and acceptability (including barriers and facilitators), that had been gained from this and previous work
Semi-structured interviews were conducted with professionals taking part in the research programme (Radley et al 2017). These included pharmacy staff and also study coordinators and principal investigators for research sites. The interviews were conducted using topic guides developed in line with the research aims and programme theory and transcribed in full for thematic analysis. These data contributed to an understanding of intervention performance, including barriers, facilitators and unintended consequences, as a component of the process evaluation. Transcripts were inductively analysed to identify emergent themes and deductively analysed to compare findings with programme theory (Radley, Tait, Dillon 2018).

2.3 The DOT-C Intervention

In the pharmacist-led pathway, pharmacists opportunistically discussed HCV infection with OST patients attending the pharmacy. Those with unknown HCV status or previous negative results were offered testing using a dried blood spot test (DBST) in the pharmacy. Those identified as having tested positively for HCV antibodies were provided with an information leaflet explaining the intervention and received a post-test discussion with the pharmacist using a standard infographic. The pharmacist assessed the participant for treatment delivered solely within the pharmacy, completing a pre-treatment checklist of medical co-morbidities, a medicines history and identifying any factors likely to impinge on treatment compliance. A peripatetic phlebotomist visited the pharmacy for safety blood tests, as in the conventional pathway and the pharmacist confirmed suitability for treatment. Where there were no contra-indications to therapy, the patient commenced treatment. In patients where there were identified contraindications or queries about suitability, the pharmacist contacted the central clinical co-ordinator for advice. Potential participants with a FIB-4 score of > 3.25 were referred on to the conventional care pathway for review (Sterling, Lissen, Clumeck, Sola, Correa... and Nelson 2006). These patients were reviewed in hospital by a medical consultant. Prescriptions for treatment in the pharmacist-led pathway were provided by a pharmacist prescriber or treatment was facilitated using a patient group direction (Medicines and Healthcare Regulatory Authority 2018). Daily monitoring was undertaken at the pharmacy, recording

any occurrence of side-effects or adverse events. Participants who did not attend the pharmacy for seven consecutive days were discontinued from care under the pathway.

2.4 Causal Loop Analysis and Diagramming

The causal loop diagram was constructed using a number of phases. The boundaries of the intended diagram were defined as the patient and organisational contributions to a cure for hepatitis C (De Pinho and Larsen 2019). Elements that might make up the diagram were defined and grouped together, drawing on published and unpublished data from the DOT-C programme, using relevant research and stakeholder experience (AR and SKI). The assumptions underlying the list of elements were discussed between authors. The representation of groups of variables was scrutinized and main drivers identified. Inter-relationships between variables were explored and flows identified. The major drivers and outcomes were built up using an interrelationship digraph and this used to consider root causes underlying the purported relationships (De Pinho yet al 2019). From this point, a causal loop diagram was developed iteratively, through discussion.

2.5 Theoretical frameworks

The analysis was informed by two theoretical frameworks. Actor network theory was used to characterize the context of drug us as the interaction of people and technology (Duff 2013). The broader context of drug use has been considered using actor network theory, which describes how subjects, activities, agencies, networks and spaces are produced in and through the activity of drug consumption. These constructs were helpful in the development of our understanding of the causal influences involved in the complex system.

Normalization process theory was used to identify the processes undertaken by pharmacy teams in incorporating the activities required by the pathway into their practice (De Bruin, O'Reill, de Bruin, O'Donnell and MacFarlane 2016). The theory utilizes the core constructs of coherence, cognitive participation, collective action and reflexive monitoring to conceptualise the processes involved with effectiveness of implementation (Murray, Treweek, Pope, MacFarlane, Ballini...and May 2010). The concepts were helpful in guiding our understanding of pharmacy team behaviours.

3.0 RESULTS

3.1 CLD development

The main objective and outcome variable for the pharmacy-led pathway is hepatitis c cure, therefore it forms the centre of the diagram (Figure1). From studying the list of potential diagram elements and identified drivers, we defined four main contributors, 1 at the organizational level (health care environment), 1 at the healthcare worker level (health worker performance) and 2 at the patient level (patient behaviours and patient environment). The health care environment contains items such as health policy, organisational drug budgets and contractor politics around remuneration. Health worker performance is comprised of elements including leadership and teamwork, attitudes to patients and relationships, multi-disciplinary team support, appropriate care provision and correct implementation of the care plan. Patient behaviours include experience of shame and disapproval, relationships with family and peers, availability of illicit drugs and health-seeking behaviour. Patient environment include interactions with the criminal justice system, housing and homelessness, income and employment and service accessibility.

3.2 Health Care Environment

The availability of direct acting antiviral medicines (DAAs) has been greatly influenced by their high procurement cost and the response of governance bodies to manage healthcare resources (Kamal-Yanni 2015). These responses have included a range of measures designed to direct the use these medicines to groups of patients conceptualised as being at greatest need and delaying use in groups thought of as having less progressive disease or with co-morbidities judged to reduce the potential for an ideal outcome (EMCDDA 2017). Some commissioners chose to cap the annual budget available to provide these treatments, in order to manage budgetary risk (Hepatitis C Trust 2018). For community pharmacy contractors who dispense these medicines for their patients, the high procurement cost has engendered risks to cash flow. Risk sharing of this factor with service commissioners was an important factor in ensuring service uptake (Community Pharmacy.Scotland 2018). Community pharmacy contractors reported some difficulties with access to medicines that were previously only used in hospital environments.

3.3 Health Worker Performance

Our interviews with pharmacy team members identified many sources of motivation. Many of the health workers were intrinsically motivated to help patients who used their services and they valued the relationships that they developed in the pharmacy (Radley,

Melville, Easton…and Dilllon 2016; Radley, Melville Tait… and Dillon 2017)). The intervention provided by the pharmacy team was most successful when pharmacists worked closely with other local services (such as phlebotomy) and where pharmacists were proactive in discussing risks with clients.

Framing the positive outcomes of testing in terms of responsibility for individual health and the health of family and community, building positive relationships and targeting stigmatising attitudes were described as factors that supported effective implementation in pharmacies. Variance in the activity seen between individual pharmacies was explained by a range of factors including staffing levels, building configuration, profile of the client group, as well as staff attitudes and the quality of relationships with patients.

Staff considered that strong leadership was necessary for pharmacy teams to be successful and that teams struggled in areas where this was lacking. Teams also struggled with staff turnover. If a motivated trained leader left the pharmacy, then this had a detrimental effect on delivery of the pathway.

"I think it is the right place to do the testing, I think we know the patients; it's easier to approach them as well. They are more likely to do the test than if somebody they don't know asked them" (Pharmacist, Pharmacy National Chain)

" I think it's because I have a special rapport with my clients, it's very much community orientated here, everyone comes in and tells you stories, you take part in their lives" (Pharmacy Support Worker, Pharmacy National Chain)

The presence of leadership and teamwork within the pharmacy created an environment where staff members were motivated to complete the task of recruiting patients.

"The most important thing is the consistency of all staff being aware of what is happening at all times and knowing the processes, the people to speak to and how to manage the patient"

(Pharmacist, Independent Pharmacy)

"When we had everything in place, myself and (staff member) practiced doing dry blood samples on each other" (Pharmacy Support Worker, Independent Pharmacy)

However, the pressure of other tasks, especially dispensing workload could impinge on the pharmacy's delivery of the intervention. The intervention worked less well where it was the responsibility of a single staff member.

"I don't have double cover and we are quite busy just with prescriptions, so it's me checking everything, but it's good doing services, but you feel that you need more time" (Pharmacist, Pharmacy National Chain).

Pharmacy staff were often keen to develop the clinical services that they were able to deliver. There was a strong motivation to diversify the range of tasks that they delivered, rather than dispensing.

3.4 Patient Behaviours

A series of contextual factors were identified through the evaluation work with study participants. These include included: expectations and experiences of stigma and discrimination; fears about confidentiality; the limited horizons of people receiving OST and the poverty they experience. Identified mechanisms that may influence uptake included the presence of established relationships with pharmacy staff; a pre-existing reason for attending the pharmacy for OST and the proximity of the pharmacy within the local community. Our discrete choice experiment clearly showed the value placed by patients of being treated with dignity and respect and of the opportunity to have care delivered in a familiar environment[27].

Patients in the pharmacy had the expectation of different treatment because of their addiction. Pharmacies often make different arrangements for the management of people prescribed OST, either to manage the numbers requiring treatment supervision or to manage the perceived risk of theft. Agency between human and non-human actors was an important determinant of behaviours of patients and of staff.

"We are all shoplifters and we have all been stealing to feed wer drug habit. See when you first get out the jail you don't get paid for about a month, so, after 3 days you are skint. Until about a month later you need to walk all the way into the toon, sometimes its 4 or 5 miles just to get your Meth, and then you have to walk home another 4 or 5 mile back or you can go shoplifting to get money for the buses or something. Ken what, its just how it is and that's how ye end up in the jail" (patient in receipt of OST, Dundee)

"You are not allowed any more than two people in the pharmacy at the same time. It doesn't matter if its rain, sleet or snow, you stand outside. She frankly told us that she doesn't want us in there when there's people in there" (patient in receipt of OST, Dundee)

People prescribed OST reported that they experienced stigma across the health system, not just in pharmacies. The established relationships with the staff in the pharmacies could often make the difference when a patient was considering whether to accept the offer of a test.

"I don't know, sometimes when you got to the hospital I don't know sometimes you feel like you are being treated differently and I just found that in here it was a more warmer environment and friendly (in the pharmacy), I wasn't treated any different, I was just

treated as me, for me personally it can understand why people wouldn't go to a hospital appointment and this is probably a better option, no probably knows why you are here, not everyone knows your business". (patient in receipt of OST, Dundee)

Fear of shame and disapproval also was apparent in relationships with family and with peers and so confidentiality in the pharmacy was an important concern.

"I've only told half of my family ken, and its kinda secret aye, because dinnae want anyone tae really ken because its a dirty disease, aye hepatitis is no like a good disease, ken whit I mean, aye "(patient in receipt of OST, Dundee)

The established relationships and trust of the pharmacy, as well as the proximity of the pharmacy within the community were recurrent and forceful themes that emerged from the interactions with the patient group

"Yean before I even started the treatment it had been discussed with me and the side effects that were known and then when the information pack came in the pharmacist had already explained to me that when that comes in first then he would read it first then he would give it to me, and that was what he done and talked it all through with me then I took the information pack away and re-read it again when I got home, so yeah everything was explained properly to me so that was fine yeah". (patient in receipt of OST, Dundee).

Participants in the qualitative work carried out during intervention development could describe concepts such as viral load from hepatitis infection and many could give accounts of poor experiences with interferon.

No, because I wanted tae get rid of it, I wanted to see if this would work, I was quite excited about it to be honest, I couldn't believe how quickly it was all happening, it was right I have got this opportunity so I have to grab it with both hands and I had to come everyday for my methadone anyway so I got both at the same time. (patient in receipt of OST, Dundee)

"Em a bit yeah, I do feel a bit more energetic I suppose, I do feel a bitty different, its kind of hard to explain, to feel a bit more motivated I suppose and a bit excited now waiting for this 12 weeks to pass so I can find out if its worked, if its not. The changes are that hopefully it has, fingers crossed. I feel a bit more positive, hopefully this will be it done". (patient in receipt of OST, Dundee)

3.5 Patient Environment

The literature describes the many psychological, physical and social aspects of living with hepatitis (Treolar and Rhodes 2009; Dowsett, Coward, Lorensetti and McKean 2017).

Experiences of stigma and discrimination are common in the environment in which people who inject drugs live, creating strong barriers to accessing HCV care and treatment (Fraser and Treolar 2006). Physical and mental fatigue arising from HCV infection discourages a normal life and frames a person's social interactions (Groessl, Weingart, Kaplan, Clark and Gifford 2008). Changes to employment status and social roles have implications for finances and morale, while relationships can be affected detrimentally, increasing feelings of isolation (Dunne and Quale 2001). Many individuals reported negative experiences with the healthcare system; themes of feeling unsupported, not having adequate information, and not feeling involved in decisions are reported (Rance and Treolar 2013). Participants may experience a reduced quality of life due to physical symptoms and all these of factors contribute to people with HCV undertaking part-time work or not working (Hill, Pfeil, Moore and Richardson 2014). Data collected by participants in the discrete choice experiment demonstrated that 43% were unemployed and 44% were receiving benefits for illness and disability (Radley et al 2019).

3.6 Hypotheses developed about causal inferences and quality improvement

Depicting the different linkages in a causal loop diagram supports the identification of reinforcing loops that continue and accelerate processes of change within a system, and balancing loops that establish organizational stability. These linkages enable hypotheses to be constructed to explain the effects seen in the intervention (Bardoel 2003).

Hypothesis 1: Teamwork and Leadership

Figure 2 depicts the two reinforcing loops (R_1 and R_2) that identify some of the factors concerned with Health Worker Performance. The hypothesis behind the reinforcing loops resembles the "Success to the Successful" archetype (Anderson and Kim 2011). The loops describe the interaction between the pharmacy team and the patient and correct implementation of the pathway.

In this hypothesis, the pharmacist leading the community pharmacy team is motivated and engaged in the provision of a new clinical service. The leadership they provide creates an ethos of positive action amongst the staff group who are given permission to approach OST users and facilitate conversations that encourage participation in the pathway; pharmacy support staff gain competency in testing and in recruitment. The time investment required to manage the pathway is traded off against other activities that may take up resources in the pharmacy. In such pharmacies, there may already be a supportive culture towards OST users and staff may already have established longitudinal positive

relationships with these clients and routinely provide advice on health matters. The pharmacy team connects with the multidisciplinary team and develops positive relationships with these actors. These factors are promoted by a pharmacy business model that values the income streams created by clinical patient services.

In the antithesis, to the above situation, the new service is contemplated as an additional burden that requires resource input. The provision of the new service may be seen as the responsibility of one person, rather than the team. The ethos created in this situation is one of the burden of competing workload and lack of staffing. The pharmacy team is inward looking and isolates itself from the influence of multi-disciplinary contacts. The pharmacy business model concentrates on prescription numbers and on maximising the volumes delivered by dispensing activities.

Hypothesis 2: Treated with Dignity and Respect

Figure 3 describes the reinforcing loops (R_3 and R_4) that identify some of the factors encountered when considering the contribution of patient behaviours. In this hypothesis, the patient has a longitudinal positive relationship with the local pharmacy team. The pharmacy responds positively to the frequent visits of the individual for OST and a dialogue around the experiences of daily living develops between the parties. The patient considers that they are treated well and values the frequent interactions with the pharmacy staff and the interest in their well-being.

The offer of a hepatitis test is therefore viewed in the context of this on-going relationship. The advantages of testing for HCV in the local pharmacy, by people that are already well-known are credible. The knowledge that all of the elements of the care pathway will be delivered within this service is reassuring, obviating the need for bus fares and journeys outside the local community.

Such interactions contrast with the experiences of stigma and disapproval that are commonly encountered in their interactions with wider society. The difficulties encountered in maintaining the requirements for a stable lifestyle such as income and accommodation, as well as conflicts and issues caused by drug use, tend to create barriers and limitations on progress made towards a cure for HCV (balancing loop B_1) (Bruggman 2012).

3.7 Hypothesis 3: Organisational Purpose

Figure 4 depicts the factors identified that influence access to DAAs and the governance processes that are created to manage the health resource (balancing loop $B_{2)}$. The high procurement price of DAAs leads government and health care organisations to put in

place measures to manage the budgetary risk. The hypothesis behind the balancing loops of this section resemble the "Limits to Success" archetype, where demand is met by a limited response and failure to develop sufficient capacity (Anderson at al 2011)
A clinical leadership response to this would be to mobilise stakeholders and partners in a systematic way, to maximise the number of people with hepatitis C that could be treated within the financial allocation (Tait et al 2017). The organized efforts and consensus approach would generate confidence that management control was being delivered and that investment was being used wisely. In this context, a narrative of deliberate success is created and a reinforcing position is obtained (R_5).

4.0 DISCUSSION

This study has brought together the evaluations carried out during the modeling, exploratory and feasibility stages of the work undertaken to develop the SuperDOT-C intervention[17]. The use of causal modelling has been advocated as a method of strengthening the evaluation and design of complex interventions (Hardeman, Sutton, Griffin, Johnston, White and Kinmonth 2005). This approach enabled identification of the positive contributions to the performance of the intervention at organisational, healthcare provider and patient level (Hoj, Jacka, Minyan, Artenie and Bruneau 2019). Our causal loop analysis led us to identify three hypotheses: the "Teamwork and Leadership" hypothesis focuses on the way that the pharmacy staff resource can be harnessed to engage patients in testing and retain them in treatment. Provision of strong leadership enables the challenges of competing workload to be managed and for OST recipients to feel welcomed. The hypothesis also recognizes the trade-off that must occur in a busy pharmacy between activities. The "Success to the Successful" archetype describes how the investment in delivering the SuperDOT-C pathway is offset against other activities that the pharmacy contractor undertakes to provide their pharmacy service.

Within pharmacies, the clinical focus of the pharmacist leading the team was instrumental in achieving greater engagement of the OST user group and of creating confidence in individual participants on the delivery of the pathway. The "Dignity and Respect" hypothesis recognizes the value of longitudinal trusting relationships propagated by pharmacy staff with individuals in the OST user group, creating reinforcing effects for the uptake of the intervention. We clearly identified that the opportunity to be treated with dignity and respect, in a trusted local service was highly valued [27]. The positive reinforcing effects of these relationships are carried through into each stage of the care cascade (Safreed-Harmon, Blach , Aleman ,Kielland, Bollerup ...and Lazarus 2019).

The analysis identified the reinforcing effects that occurred when clinical leadership was demonstrated, both at an organisational level and at a local level within the pharmacy. At an organisational level, clinical leadership was provided for the SuperDOT-C intervention through the regional managed care network, which promoted and supported delivery of a range of interventions aimed at elimination of HCV (Tait et al 2017). The leadership exhibited through the managed care network could mitigate some of the balancing effects of organisational risk management. Leadership and the description of common purpose between stakeholders was able to some extent overcome the "Limits to Success"

archetype (where success attracts more resources, despite the needs of lower performing groups) and enable the development of capacity and focus.

The environment in which the patient lives has a pervasive effect on engagement with care, with the availability of employment, housing and services determining whether accessing heath care is a priority. Experiences of stigma and discrimination are common for people who inject drugs, creating strong barriers to accessing HCV care and treatment (Treolar, Rance and Backmund 2013). The adverse effects of drug use and the associated poverty, created balancing effects that discouraged engagement with testing and treatment for HCV.

A number of studies are currently being undertaken that demonstrate the feasibility of decentralising care and providing local services with reach into communities of people infected with HCV. Such pathways may increase uptake of treatment and can provide sustained viral responses equivalent to those attained in specialist centres (Wade, Doyle, Gane, Stedman, Draper...and Hellard 2018; Swan , Cullen, Macias, Oprea, Story...and Lambert 2018; Grebely, Alavi, Micallef, Dunlop, Balcomb...and Dore 2016). SuperDOT-C utilised pharmacy staff in order to increase reach and access. Examples of pharmacist-driven models of hepatitis C virus (HCV) care are now described from multiple single-center and multicenter retrospective and prospective cohorts in a range of settings (Koren, Zuckerman, Teply, Nabulsi, Lee and Martin 2018; David, David, Essex, Deming, Qualls and Mera 2017; McNamara, Budlong, Peterson and Tisthammer 2018; Ho, Fong, Tran, Gonzalez, Chung... and Morgan 2017), but achievement of the WHO target on elimination requires that a range of staff groups with skills and opportunities contribute. This study provides some evidence that models of care are likely to be most effective when wielding positive and trusting relationships with the groups of people who are infected with HCV. Leadership at individual practice and organizational level enables available resources to be directed most productively at achieving elimination.

Causal loop diagrams are a qualitative representation of a complex interactive system. Use of this technique has a number of limitations (Schaffernicht 2010). The diagramming technique may lack precision with a tendency to over-aggregate variables, so that several items may be hidden behind a single term. In a real world complex system, there may be a loss of distinction between stock and flow variables and the relationships between events and behaviours must be used in a pragmatic way. In developing a causal loop diagram, boundaries must be set that mark the limit of the relationships to be considered. Such limits necessarily mean that the diagram is an approximation of the real world situation.

However, causal loop diagrams describe an explicit model and use is intended to aid the understanding of the complex system and the interactions of variables within and between levels (Cavana et al 2004).

CONCLUSION

This study provides some evidence that models of care are likely to be most effective when wielding positive and trusting relationships with the groups of people who are infected with HCV. Leadership at individual practice and organizational level enables available resources to be directed most productively at achieving elimination. The most important dimension of complexity is the context into which the intervention is introduced (Hardeman et al 2005). The community in which the individual lives, and the support and resources available to them are critical considerations when implementing interventions to eliminate HCV. In a complex adaptive system where the system attempts to retain equilibrium, each of the reinforcing and balancing relationships should be optimised to enable the best chance of achieving success.

The references to this paper are located in the manuscript provided in Appendix 9.8

Figure 1: The set-up of the causal loop diagram

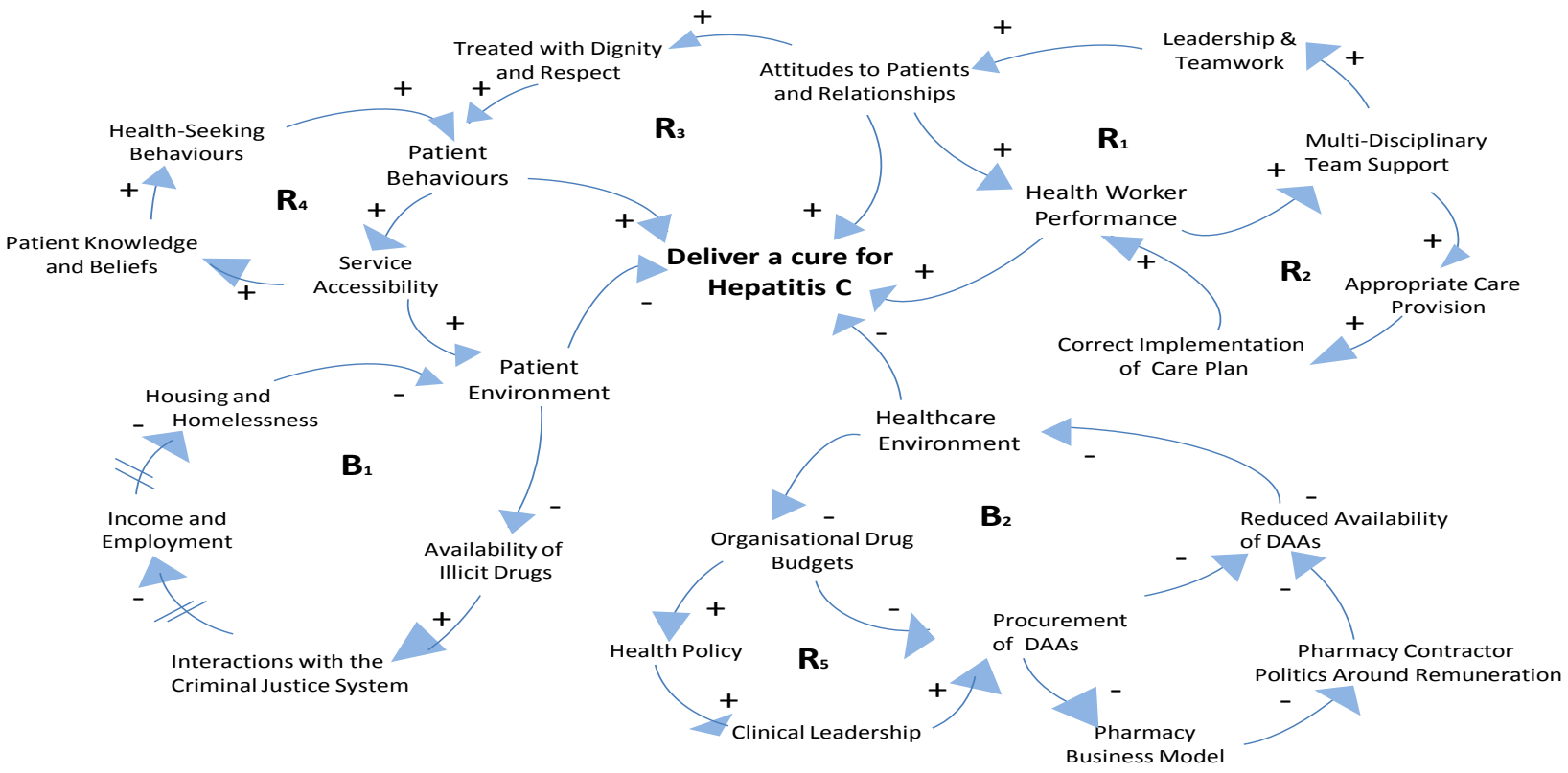


Figure 2: Reinforcing loops for Pharmacy Performance

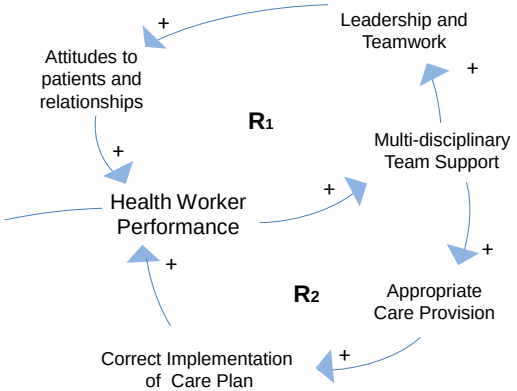


Figure 3: Reinforcing Loops for Patients Behaviours

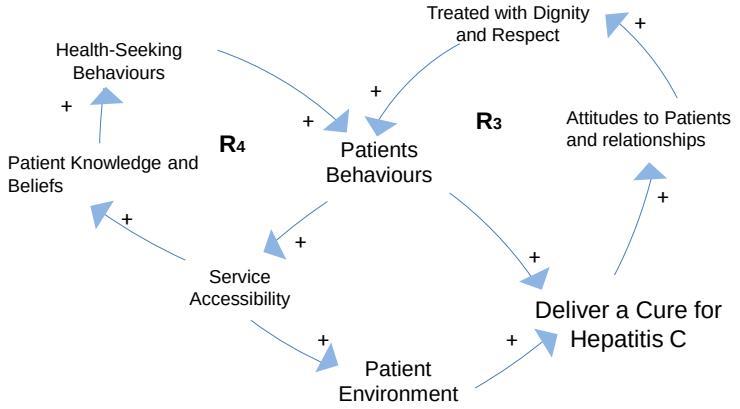
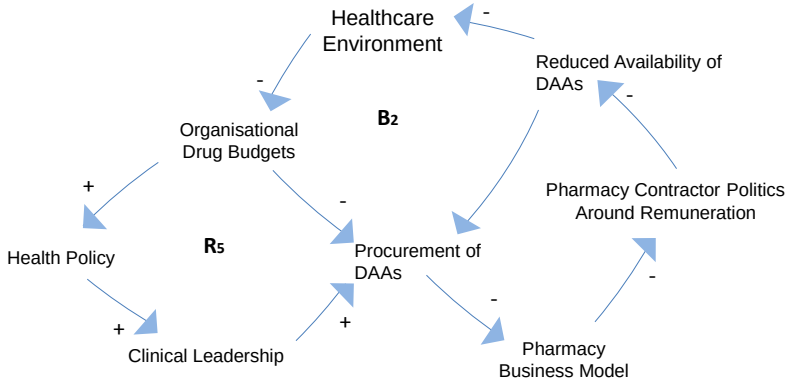


Figure 4: Balancing and Reinforcing Loops for Healthcare Environment



6.2 Critical Reflection

The systems-thinking analysis comprising the content of this chapter was undertaken as a reflection and summary of the SuperDOT-C research programme. The process of analysis required that a high level view of the series of the literature reviews and study evidence was taken, so that the components determining the key ingredients of the intervention could be identified. The process of analysis required discussion and reflection with colleagues and are-visiting of the data produced by the studies undertake during the development of the intervention. The process was satisfying to undertake, as a final chapter of this thesis, since it enabled examination and contemplation of the learning that had been achieved and review of the development and implementation of the methods that had been employed.

6.1.1 Critique of methods

A variety of methodological approaches have been suggested as ways to enhance the understanding of the processes involved in the effectiveness of an intervention. In this thesis, some of the techniques utilised in theory-driven evaluation and realist evaluation have been used to underpin exploratory studies. Implementation processes for pharmacy staff have been considered using an application of change theory. The concepts of person, place and time seen as part of a realist approach, as well as the complimentary ideas described through actor-network theory were key foundations of the analysis.

A systems-thinking approach was selected for this study as a useful way of considering the nature of a complex adaptive system in an integrated health system in Scotland. The application of this approach requires that a wider perspective is taken and that interactions between components, feedback effects and positive reinforcement within a larger system are considered. The use of causal loop diagramming proved to be a useful technique in visualising the assumptions that had been made about the dynamic system. The linking and interaction of components and the assignment of polarity enabled a better understanding to be gained of the behaviour of the system and its agents.

6.1.2 Critique of analysis

The analysis requires that decisions are made through discussions with co-researchers and that agreement on the components of the causal loop diagram, as well as the direction of travel and polarity of the interaction are obtained. The findings of the analysis are therefore a result of these discussions and are based on a thorough examination of the

supporting evidence. Other researchers considering similar data might have different conversations and agree a different profile of components and interactions.

Causal loop diagramming requires that a series of assumptions and approximations are made. The extent of the causal loop is achieved through a decision about how far out to proceed. The interaction of this system with wider systems and wider effects means that all diagrams are limited by their agreed extent. Similarly, the components of the diagram are also approximations, since a single term may very well be a compound term made up of several different functions.

However this approach, to visualise the assumptions made about causal inferences underlying the intervention was valuable and enabled hypotheses about the key ingredients of the intervention to be described. The analysis enabled the effects seen around good quality relationships to be recognised and the limiting factors around patient environment and organisational budgets to be highlighted.

CHAPTER 7

DISCUSSION AND CONCLUSION

This chapter reviews the findings that have been produced and reflects on their meaning in terms of the development of the complex intervention, as well as the limitations that the methods selected for the studies used have brought. In addition, a narrative linking together the different studies that discusses the methodological and conceptual issues is included.

The research programme described in this thesis follows the process of development of a complex intervention to provide testing and treatment of HCV infection in people receiving OST from community pharmacies. The programme, consisted of a series of eight studies, which were undertaken to understand the context for delivery; evaluate service users and provider preferences for the shape of the service; pilot the delivery of the intervention and then evaluate its effectiveness; analyse the findings of the programme to form ideas about what the essential ingredients underlying the success of the intervention.

At many stages of the research programme I interacted with the service user group and the people providing the services that they relied upon. I also spent time in community pharmacies and observed the daily work routines and systems that are used to provide the care to the patients using these practices.

During this work I became very aware of the vulnerabilities of the group of people who inject drugs: the fragility of their home circumstances and accommodation; their reliance on supporting services for food and income and shelter because of poverty they live with; the everyday traumas and casual violence they experience and the additional burden of stigma and discrimination that society places upon them. However I also was engaged by the candour that they used in discussing their experiences and by their openness and friendliness when asked about their situation.

As part of this work I spent time talking to pharmacy staff. Community pharmacies are contracted to provide pharmacy services and are remunerated mainly for dispensing services, with other clinical services being largely subsidised by this main activity. Most staff in community pharmacies tried very hard to provide caring and high quality services to their patients within the constraints of their training and the pharmacy contract. I

observed many examples of excellent care and of strong relationships between staff and the people receiving their services

7.1 Critical Reflection

This thesis made use of the Medical Research Councils guidance on developing and evaluating complex interventions (Craig, Dieppe et al 2006) as a structure to steer the research programme. The guidance provided advice on the process of understanding how an intervention worked within a specific context and gave case histories to illustrate the processes that were features of competent research. There was a development from the initial version of the guidance (MRC 2000) to the newer guidance in 2006, which suggested that development processes were an iterative rather than a progressive increase in understanding. In this programme, I found that each study I undertook increased my understanding and deepened my appreciation of the effect of context. Triangulation is a concept that requires that more than one method of data collection or evaluation is employed to answer a research question. The data achieved from these triangulating activities are compared with the objective of providing a more comprehensive understanding of the mechanisms at work (Rosaline 2008). In this programme, understanding was increased through following this way of working and used to generate ideas about the "essential ingredients" of the intervention and how these ideas might be refined in the light of new data (Rutter, Savona et al, 2017).

A further important component of the approach taken was the activities undertaken to understand the views of service users. The ideas around patient and public involvement in the design and implementation of research were very much appreciated in this programme. The first stage of designing the intervention was based around listening to the voices of service users and working to understand their priorities for service provision.

The recognition of Actor Network Theory was a key step forward in helping understanding of the way that people interacted with the environment and the human systems that had been put in place (Latour, 2005). Through the concepts contained in this approach, a better understanding of the meaning of the "methadone queue" in pharmacies was gained and the narrative provided by both service users and service providers could be contextualised within an explanatory framework.

The researcher's position and background and the effect it has on the research, in terms of construction of the research and interpretation of the data it generates (Rosaline 2008) is an important point of reflection. Reflexivity is an evaluative process by which the research reflects on their own beliefs and opinions with regard to the research and considers the biases that this may confirm on the study. In this programme, my professional background and training in professional behaviours were quickly identified as guiding my approaches and attitudes to research participants. Other influences may include age, sex, race, religion, sexuality, politics and life experiences (Berger, 2015). In this programme, observation of the experiences and study of participant narratives made my empathy for and understanding of the lives of participants in the research much greater.

The studies contained in this thesis were undertaken with a group of people understood to be vulnerable in a number of ways. There was the potential to have to tell them upsetting news that might disturb their fragile relationships or bring them into contact with people and circumstances that they might find distressing. This was managed from the beginning of the programme by working with more experienced staff who were familiar with the procedures that could be used to manage these risks. By working to a great extent from community pharmacies, we also were able to meet with these people in a familiar environment where they were able to see familiar faces. Reflecting back on the interaction with the patients whose experiences and lives provided the data for these studies, these participants were not distressed by recounting their experiences, even though some of the accounts they described would have been traumatic. They were generally willing to give up their time and share their stories and I am most grateful to them.

7.1.1 Developing and evaluating a complex intervention in community pharmacy

Complex interventions are widely used across many sectors of public services, including public health practice, education, transport and housing. Within the health service, such interventions may have important consequences for the health of target populations and for communities and families. Current guidance from the Medical Research Council, recommends the use of a variety of approaches to addressing the methodological and practical challenges faced when establishing a complex intervention (Craig, Dieppe et al 2006). This advice suggests that greater attention is given to piloting and development work, that a less linear model of evaluating processes is used, that process and outcomes

evaluations are integrated and that insights provided by the theory of complex adaptive systems are utilised (Rutter, Savona et al, 2017).

This thesis has sought to utilise the Medical Research Council's recommendations for developing and evaluating a complex intervention. It has employed a range of different methodological approaches to support the accumulation of knowledge and insights into how a care pathway to deliver testing and treatment of HCV infection might operate in a community pharmacy.

The contemporary history of pharmacy is one in which the traditional work practices and mechanics of medicines dispensing have been infiltrated by technology. Barcode readers and robotic dispensing have largely replaced the need for medicines stock manipulation and accuracy checking of prescriptions and this existential threat to the profession has been debated widely (Anderson 2007). There has been a lack of evidence of the beneficial outcomes to patients of the care provided by pharmacies and the emerging area of improving public health has been used for evidence of the continued relevance of pharmacy (Anderson, Blenkinsopp, Armstrong, 2009). There are also a range of recognised advantages that pharmacies bring to health care: the location of pharmacies in the high street; the proximity of pharmacies within disadvantaged neighbourhoods; the access to a registered health profession without appointment and the longitudinal relationships that develop between pharmacies and the public; the access to medication to treat a widening range of conditions; the anonymity of usage of a pharmacy where no appointment is needed to access advice (Lowrie, Morrison et al, 2015). The contractual basis of community pharmacy also brings a range of different factors into the practice environment. As with general medical practitioners, general dental practitioners, opticians and podiatrists, community pharmacists are contractor bodies practising according to a nationally negotiated contract within standard terms and conditions. Additionally in pharmacy, a commercial offer is also in place, whereby customers can purchase a range of products outside of the nationally funded provision. This dual identity has led to tensions between the clinical aspirations of the profession and the commercial necessity of delivering profit. The development of an intervention in community pharmacy therefore is undertaken with an awareness of all of these factors.

7.1.2 Delivering Hepatitis C testing and Treatment in Community and Primary Care Settings

Publication 1 – Systematic review and meta-analysis of care pathways evaluated using direct-acting antiviral medicines

The systematic review and meta-analysis of community and primary care based HCV testing and treatment services, using DAAs, found that across a broad base of locations, more people access care when it was provided with other care that they engaged with. The study also identified that similar outcomes were achievable in primary care and community-based settings to those identified in specialist centres (Wade, Veronese et al 2016).

However, identified studies showed large amounts of heterogeneity. There was wide variation in the numbers of participants recruited and a lack of direct comparisons with care pathways in specialist centres. GRADE assessments showed evidence for the uptake of HCV treatment (medium), evidence for completion of HCV treatment (low) and evidence for achievement of a virological cure (SVR) at 12 weeks (medium). There was a lack of high quality definitive experimental studies that could provide evidence of a definitive effect for decentralised services that used a task-shifting approach. This finding demonstrated a gap in the evidence base and provided the rationale for undertaking this course of study. The systematic review suggested that services sited in community setting are feasible and can encourage a vulnerable group of people prescribed OST to access care.

The introduction of direct-acting antiviral medicines represented a huge change in the ability of health services to cure HCV and led to the inclusion of the elimination of HCV as a public health concern being included in the Sustainable development Goals (Goal 3.3) (WHO, 2016 a). The uptake of these new medicines was initially by specialist services, used to managing the more problematic and difficult to manage regimes containing interferon and ribavirin (Tait, Wang et al, 2017). The shift of care provision to primary care sites was initially reported through poster presentation and with observation study and even case report formats (Bajis, Dore et al, 2017). The novelty of the therapeutic area provided confidence that there was a question worth answering and that undertaking a programme of research to develop an intervention would likely to be fruitful. In parallel to these findings, the lack of good quality pharmacy-based research in this area also provided reassurance.

Despite the assessment that this was a new area with very few high quality reliable studies on the subject, our literature review revealed over 10,000 hits before de-duplication. There was a significant amount of work required to assess the identified studies and I gained a much better appreciation of what makes a good and a bad manuscript through this exercise. I also gained a much better awareness of how reporting guidelines and standardisation of reporting makes research more accessible and easy to interpret. The evidence indicated that there would be a place for a definitive study in which DAAs were deployed by non-specialist personnel within community environments.

7.1.3 Development and Modelling of an Intervention in Community Pharmacy

Publication 2- Focus group series evaluating the experiences of service users of pharmacy services

Publication 3 – Discrete choice experiment to evaluate features of a preferred service

Publication 4- Quasi-experimental study to evaluate whether testing in pharmacies was feasible

This phase of the research programme was fundamental in developing a theoretical understanding of the likely process of change that would be utilised by the planned intervention. The research resulting in these three publications was enabled by a Fellowship gained from Gilead, a pharmaceutical company who manufacture DAAs to treat HCV infection.

The focus group series enabled a description of the social context surrounding attendance at a community pharmacy to be gained. The participants in this study described how they were often treated differently from other people who accessed care in the pharmacy. The way delivery of OST was arranged in the pharmacy, often denied patients the right to confidentiality and high numbers of OST recipients attending a pharmacy could cause issues when patients requiring other services were attending the pharmacy at the same time. Participants readily identified poor experiences of care, yet valued some of the good relationships built up over time with pharmacy staff. Constructive attitudes and humanity from pharmacy staff could contribute to progression towards recovery and help address the inequalities experienced by this group (Read, Lothian, 2017).

The focus group series drew on the insights of service users experiencing care within community pharmacies. Participants in this study could readily describe their experiences, both good and bad. The group dynamic helped facilitate description of the experiences and also helped in gaining peer recognition of the discourse (Bloor, Frankland et al, 2002). The approach also led to a group narrative in some respects, where dominant

voices talking about resonating themes tended to take up the discussion. Several strategies were used to overcome this limitation, including awareness of the facilitator, gaining perspectives on findings from feedback of other groups, use of specific groups – women's groups and peer supporters – to gain further insights into the experiences of care. The context provided by the study and the insights it provided into the interaction between person, place and time were a key stage of intervention development. The exercise meant that the research could be grounded within the experiences of people's lives.

In order to access the people who would be able to give the most useful discourse, we arranged groups in church halls and recovery cafes where support services were accessed. Links were made with service staff who circulated leaflets and asked people if they were interested in attending. Once participants understood what we wished to talk about, there was no difficulty in generating a relevant conversation. A greater challenge was facilitating a balanced narrative in which each participant had the opportunity to contribute their perspective. In achieving this balance, a purposive strategy to undertake a women's group and a peer mentor group was undertaken, to increase the prospect of a valid and generalisable outcome (Bloor, Frankland et al, 2002). The findings from this study amply demonstrate the range of experiences of service users visiting pharmacies. The views expressed by participants regarding those things that went wrong with pharmacy services and how pharmacy services could be valued provided the material to start the next study – A discrete choice experiment. We used these data to identify the variables we could use as attributes to describe an ideal service from the perspective of service users. The experiences of stigma and discrimination within pharmacies, that were highlighted in the focus groups, led us to formulate the attribute of "dignity and respect" in the subsequent econometric study.

The discrete choice experiment utilised the attributes of a service, identified through this development work, to further assess the relative preferences and to try and quantify the value placed on different parameters (De BekkerGrob, Ryan and Gerard, 2012). The study provided clear evidence that being treated with dignity and respect was a critical factor in service acceptability. The study also provided supporting evidence that care provided in a person's "own pharmacy" were strongly favoured.

The study utilised a standard format for choice presentation. The language used to describe the choices was piloted using a "speak aloud" process to test understanding and assess cognitive burden. The issue of stigma and discrimination was very real to participants. Many of them had experienced poor treatment in the care they had received

during their treatment careers and responded very strongly to the suggestion of "dignity and respect". The strength of this response may have meant that other less important attributes were given less consideration. Nonetheless, the appreciation of dignity and respect, plus the way care provision in the participants' "own pharmacy" was valued gave clear indications on how an intervention might be structured.

The way the respondents reacted to the suggestion of being treated with dignity and respect was striking and dominated the narrative of the interviews. The response was so strong, that it usually made the other attributes contained in the questionnaire of much lesser importance. The response to "own pharmacy" was also strong and may have reflected that the participant had found a safe place to visit to gain their methadone. This finding gave reassurance that service users would accept the offer of a test from their own pharmacy. A consequence of the finding was that when pharmacy staff were trained to offer testing, we set out a standard script in an infographic that could be used to set the tone of the conversation. Our training emphasised the need to use the day-to-day interactions with service users to mention the possibility of testing and we also presented a lot of material that was designed to heighten awareness of the potential for stigmatising behaviours.

The quasi-experimental evaluation of dried blood spot testing in pharmacies showed that this technique could be delivered by pharmacy staff and that service users were prepared to be tested in the pharmacy environment. Interviews with service users of the intervention provided further insights into the context for delivery, about fears and anxieties about a diagnosis and treatment and about feeling of shame around having been infected with HCV. Service providers also provided insights into the ingredients for success, including strong leadership and teamwork. They were often enthusiastic about undertaking a new role, but some were unfamiliar with a more hands-on care approach.

The observational study had a number of limitations, as well as benefits (Craig, Cooper 2012). The primary limitation of the study was the small number of participating pharmacies in a single location and the lack of experimental procedures to limit systematic selection bias. Some variance in uptake of the intervention was observed between pharmacies. This observation is commonplace across regular day-to-day services such as provision of smoking cessation, as well as with this intervention. The variance is usually conceptualised and explained by the different business models in pharmacies and by the different staffing levels that pharmacies employ to deliver their contract. Further

variables include the leadership provided by the pharmacist in undertaken clinical work and by the motivation of staff team members: the ethos within the pharmacy.

This study design provided a rapid and straightforward way to test the feasibility of testing and provided the research programme with reassurance that the intervention was acceptable and could be delivered by pharmacies. The finding that service users were twice as likely to accept the offer of a test from pharmacy staff as from specialist nurses working in community setting and from third sector support organisations was interesting and provided insights into the potential of a pharmacy-based intervention for improving health.

The process of contracting with community pharmacy companies to undertake research was new to me. The agreement process required that I work simultaneously with the contractor representative body, individual contractor companies and staff within pharmacies in order to gain agreement in participation. This process was not only about staff governance and professional standards, but also about guaranteeing the return on investment of staff time by the company and ensuring that insurance covered the activity. Training the pharmacies to undertake the blood test also meant that I had to be competent myself. The study also required that I become competent in performing standard statistical tests in order to analyse data generated and to use reporting guidance to write manuscript of an acceptable standard. The planning of research outcome using a logic model as a planning tool was also a new skill to be applied.

The evidence provided from the quantitative data of testing uptake and the process evaluation conducted with service users and staff provided sufficient justification to comme.ce the planning for a feasibility study of the entire testing and treatment pathway.

7.1.4 Feasibility Assessment and Evaluation of a Care Pathway for Testing and Treatment in Community Pharmacies

Publication 5 – Feasibility cluster trial of the pharmacy pathway compared to the standard of care

Publication 6 – Published protocol for the multi-centre randomised controlled trial

Publication 7 – Outcomes from the definitive multi-centre trial of the pharmacy pathway compared to the standard of care

This phase of the research programme assessed the feasibility of the intervention and measured the outcomes associated with deployment of the intervention in different locations (Craig, Dieppe 2006). The research in this section was undertaken using a further grant from Gilead for the feasibility RCT and by a funding partnership with the

Scottish Government, and with Gilead and Bristol Myers Squibb, donating free DDAs for the treatment of study participants.

The feasibility study looked to deploy all the elements of the intervention and test how pharmacies could support the delivery of testing and treatment as part of the efforts of the multi-disciplinary team. The experimental design for the study was utilised to address potential selection bias and give some indication of the effect size that might be achieved in a definitive trial (Eldridge, Lancaster, 2012). The study confirmed that participants in a pharmacist-led pathway were more likely to take a DBST and that attrition from the pathway was lower at all points than for the conventional pathway of care. The study also demonstrated the loss of participants from the pharmacy pathway when they were asked to attend a different site for phlebotomy. Service users had mainly positive perceptions of the care provided. They thought that pharmacies were a good place to receive care where they enjoyed positive relationships with staff; they already had a reason for attending and did not need bus fare to attend the hospital. Staff members had strong views about the value of leadership and teamwork in creating an environment for performance. Good quality relationships with patients were a key ingredient in engaging them in testing and treatment. A comparison of the costs of providing care in pharmacies and in conventional care pathways demonstrated that the pharmacy pathway was associated with lower costs. The feasibility study was not able to determine a significant difference for the primary endpoint of virological cure (SVR12). This was because of the attrition caused by offsite phlebotomy, because of the number of participants with a genotype 3 infection (who could not be treated with study drugs) and because of a larger number of participants than expected who attained spontaneous clearance of virus. However, the cascade of care developed through the programme demonstrated that a worthwhile effect was likely to be achieved in a larger study. This evidence helped us to further refine our pathway, in particular creating the facility for peripatetic phlebotomists to take assessment blood tests within pharmacies instead of asking participants to visit another site. We also were required to develop a patient group direction for DDA prescribing, since there was not the same availability of pharmacist prescribers in Grampian and Glasgow, as in Tayside ("MHRA", 2019)

The multi-centre cluster randomised trial was able to utilise developments in medicines technology, so that genotype 3 infections could be treated with a simple oral regimen of direct-acting antiviral drugs: these medicines were not available when the feasibility study was planned and only genotype one infections could be treated in this way.

The multi-centre study was also able to demonstrate a significant difference for the primary outcome. A greater number of participants in the trial achieved virological cure (SVR 12) in the pharmacist-led arm, than for the conventional care arm. This difference was apparent at the recruitment for testing stage and this was maintained through the care cascade.

The deployment of the intervention in different locations meant a large increase in complexity for implementation and evaluation. The different contexts and cultures of each health board site meant that training and some procedures had to be adapted for the local situation. An example would be the administrative bureaucracy required to enable pharmacy staff to perform DBSTs. In Tayside, a simple training course across 90 minutes was sufficient, whereas in Grampian, a course over several days, with assessment and certification was required.

The pharmacist-led pathway provided advantages across the care pathway in terms of recruitment and retention. The key ingredients identified during intervention development: trusting relationships, local care in the community; no requirement to move to access treatment at different sites; treatment with dignity were deployed in the design of the complex intervention and contributed to demonstration of positive outcomes across the care pathway (Gartlehner, Hansen, 2006).

A range of new learning was required for this phase of the research programme. Preparing submissions for research ethics and using the IRAS system effectively was a new experience, as was working with Sponsors and Research and Development departments. The governance requirements were more than this though and included writing contracts with university solicitors to engage pharmacy companies and constructing service specifications to describe how we expected the pharmacies to act. The approval of the contracts and documentation by the pharmacy companies Superintendent Offices (professional governance) caused a long delay in finalisation of arrangements and study implementation. The delay amounted to around eight months, meaning that some of our donated drug had expired and that we had to ask for further supplies. The politics of the project meant that we also had to gain support from the policy leads at government and liaise with professional Board leads A further complication that we had not appreciated was around staff turnover in pharmacies. Pharmacist and their staff often move jobs to another pharmacy and this created difficulties for study management, requiring us to re-train on several occasions: two pharmacists moved from one pharmacy in the study to another pharmacy also in the study, which was less problematic.

The evidence provided through this programme demonstrated that the pharmacy-led intervention enabled approximately twice as many people prescribed OST to achieve a virological cure as the standard of care. This finding was coherent with the understanding and data collected from development work and fitted well with our theory about the value of being treated with dignity and respect and in offering treatment in a well-known and familiar environment. The piloting and feasibility work provided a rich source of data from which to undertake the final part of the research programme that formulated hypotheses about why the intervention had succeeded.

7.1.5 Mapping of Causal Inferences Identified during the Development and Evaluation of a Complex Public Health Intervention

Publication 8 – Systems-thinking analysis of the hypothesised causal mechanisms underpinning intervention effectiveness.

As part of the evaluation of the SuperDOT-C intervention, a systems-thinking approach drawn from the theory of complex adaptive systems was utilised (Peters, 2014). This study utilised causal loop diagramming to describe the components surrounding the intervention and to describe the possible interactions and linkages between these. From analysis of these diagrams, hypotheses were formed on the potential causal mechanisms that formed the key ingredients in the success of the intervention. This analysis utilised evidence from the surrounding literature as well as data produced through the programme of research to define important components and suggest their inter-relationships. Several reinforcing relationships were suggested. These included the relationships between the pharmacy and the participants. The support from the multi-disciplinary team to the pharmacy was important in creating an integrated perspective to care. Trust in the pharmacy and the environment surrounding care provision, encouraged health-seeking behaviours and engagement. Several inhibiting factors were also identified. The high cost of the anti-viral drugs placed budgetary constraints on the availability of the medicines. The cost also had the potential to disrupt the business models of the pharmacy and the cash flow that they required. These factors could be mitigated through organisational leadership provided through the managed care network. Environmental factors that included the availability of illicit drugs, of employment and housing, also had profound effects on the ability of participants to engage in the intervention.

This type of analytical approach has well recognised limitations (Carey, Malbon et al, 2015). These include the definition of the boundaries of the analysis and the effects of describing a number of variables under one component. Assessment of the polarity of

effect may be problematic, where stock and flow variables are mapped to health behaviours. Nonetheless, the analysis provided a useful summation of the research programme and helped to make clear insights and inferences that had been identified. The construction of the pathway required a group interaction from the research team with active discussion of the way that the effects were mapped and which direction the effect travelled. The diagram was constructed in staged with a consensus forming around a final draft. The end point provided a suitable summary of the work that had been undertaken and formed a graphical representation of all we had learned.

7.1.6 Future Development of the Programme

A number of tasks remain to be completed in order to bring this programme of research to a natural conclusion. At the time of submission, six manuscripts from eight drafted have been published in relevant peer reviewed journals, but two remain to be brought into the public domain. These are the papers describing the findings of SuperDOT-C and also the Systems-thinking analysis.

A further series of papers require to be drafted in order to complete the publication of work that has been undertaken. These are:

- A reflection on the learning achieved from carrying out research in community pharmacy with a presentation of the particular challenges that this environment provides.
- A health economic analysis of the pharmacy-led pathway
- A presentation of the qualitative themes identified through the three process evaluations that were undertaken at points within the programme.

It is hoped that this further work will provide a satisfactory summation of the development and evaluation of a complex intervention.

7.2 Conclusions

The programme of research has deployed a variety of qualitative and quantitative approaches to gain an understanding of the way that the SuperDOT-C intervention is likely to perform, when used to test and treat people infected with HCV who are prescribed OST. The insights gained have enabled design, implementation and evaluation of a complex intervention. Evaluation of the SuperDOT-C intervention in a definitive multi-centre trial provides evidence that a greater number of participants in the trial achieved virological cure (SVR 12) in the pharmacist-led arm, than for the conventional care arm.

Information gained during a series of development and feasibility studies has provided insights into the key ingredients that are likely to be necessary for successful implementation. These ingredients are thought to concern the quality of relationship between participant and provided, the supportive nature of the community in which the service user lives and the way that organisations identify the need for vulnerable groups to access care and treatment in an equitable way.

This thesis therefore contributes to the body of knowledge supporting the delivery of the WHO's guidance on the screening, care and treatment of persons with chronic hepatitis c infection (WHO 2016c) and the aspiration set out in the Sustainable Development Goals (3.3) for elimination of Hepatitis C as a public health concern by 2030 (WHO 2016a).

7.3 Summary of knowledge and evidence contributions of the thesis to policy development and scholarship

Overview of the case presented

Primary Research Objective:

Can a pharmacist-led care pathway designed to test and treat HCV infection in people prescribed OST, increase the numbers of this population who access treatment and cure for Hepatitis C?

This programme of research has modelled, established and evaluated a testing and treatment pathway for people with HCV infection in community pharmacy. A review of evidence and policy has described the case for task-shifting of care to the wider multi-disciplinary team and of decentralising care to community locations. A systematic literature review identified and evaluated published examples of where task-shifting and decentralisation had been evaluated and found evidence that these strategies may increase access to care whilst maintaining cure rates when direct-acting antiviral drugs are prescribed.

A series of studies examined important factors that might contribute to the uptake of a pharmacist-led intervention, including service user and service provider views. Experimental work evaluated the intervention, both from a feasibility perspective and also looking of the generalisability of the intervention in different contexts. Evidence is provided that a pharmacist-led care pathway can increase the numbers of this population who access treatment and cure for Hepatitis C.

Secondary Questions:

What are the views and experiences of people who access pharmacy services to receive OST?

A series of studies examined the experience of healthcare from the service-user perspective. These studies recorded both good and unsatisfactory aspects of the experience of care. The pervasive experiences of stigma and discrimination encountered when using pharmacy services were documented using a focus group series. The way that the pharmacy service was organised and the attitudes and actions of staff were important factors that impinged upon the satisfaction of people using these services. People who access pharmacy services often valued the care provided by a pharmacy and its place in the local community.

What are the important factors to be considered in the design of a pharmacist-led care pathway, from the perspective of the service-user population?

Attributes identified from the focus group series were utilised to undertake a discrete choice experiment. The questionnaire administered as part of the discrete choice experiment demonstrated that the most important feature of a service was being treated with dignity and respect. The relationship established with a trusted pharmacy was also valued. Waiting time for results and travelling distance were also important factors in creating a treatment pathway that would be appreciated by service users.

Can a pharmacy-based testing service for HCV infection encourage the target population of service-users to take a test for blood borne viruses (BBVs)?

A pilot project to establish dried blood spot testing in a group of pharmacies was evaluated as a quasi-experimental model and views of service users and service providers were obtained. The pilot provided some evidence that testing could be provided by pharmacy staff within a pharmacy and that more people might take up the offer of a test. Factors such as good relationships with pharmacy staff and the need to attend the pharmacy regularly may have increased the uptake of testing.

Is the delivery of a pharmacist-led pathway to deliver testing and treatment for HCV feasible? How do service providers describe the provision of this service?

A feasibility trial was undertaken to evaluate whether the pharmacist-led care pathway could be delivered. Alongside this cluster randomised controlled trial, a process evaluation was undertaken. The trial provided some evidence that service users would accept the offer of care provision from and pharmacy and that the method of HCV diagnosis, assessment for treatment and delivery of medication, could be successfully delivered in the pharmacy. Previous work had established that the place of the pharmacy within the community and the development of trusting relationships were important. The feasibility trial demonstrated that more service users were retained on the care pathway when care was provided from that one location. Attempts to move patients into other locations to receive care resulted in increased attrition from the pathway. Pharmacy staff in general appreciated the opportunity to develop their practice and valued the ability to provide more care to the service user group. Factors such as staffing complement and dispensing workload could impinge on their ability to deliver the pathway.

What are the barriers and facilitators identified that impinge on the access to and delivery of effective care?

A review of published evidence and policy and data obtained during this programme were utilised in a systems-thinking approach to reflect upon possible causal mechanisms for the intervention. The relationships between identified components were described in a causal loop diagram and this was used to formulate hypothesise about how different factors might inhibit or promote the effectiveness of the intervention. Facilitators to the success of the intervention included positive patient relationships, proximity to the community and role enhancement as factors promoting uptake of the care pathway. Barriers to the uptake of the intervention included factors such as experience of stigma and fear of treatment side-effects, but also the factors such as homelessness, healthcare policy and budgetary restraints.

7.3.1 Summary of research contributions

The research included in this thesis has provided evidence that a pharmacist-led care pathway designed to test and treat HCV infection in people prescribed OST, can increase the numbers of this population who access treatment and cure for Hepatitis C. It has identified the role that stigma and discrimination can play in provision of care. It has shown that positive relationships between providers and service users can increase health-seeking behaviours in a vulnerable patient group who experience profound health inequalities. It has shown that the introduction of new medicines technology can decrease the need to deliver care from hospitals and that such technology can enable non-specialist staff to become an integrated component of care provision.

Its global evidence contributions include:

-The identification of a fragmented but developing pool of evidence indicating that hepatitis care can be delivered in primary care and community settings, by non-specialist staff

-The identification that service design that utilises service users perspectives may lead to the development of a more effective intervention.

-That inertia in established hospital-based care pathways may be reducing the number of people with HCV infection that are able to access care and therefore cure of their condition.

-That developing a complex intervention requires a systematic approach to gain an understanding of context, assess feasibility, assess effectiveness, measure outcomes and understand processes.

-That generation of evidence demonstrating the delivery of effective is a strategy that supports policy development

-That generation of evidence from real-world, multi-stakeholder engagement processes requires a range of additional skills to those recognised as central to delivery of high-quality research.

Its knowledge translation impacts include:

-Support for the WHO recommendations for the care and treatment of persons diagnosed with chronic hepatitis C virus infection

-Support for the Scottish Government's policy ambition to eliminate hepatitis c infection as a public health concern from Scotland by 2025 (through participation in the Short Life Working Group Report, "Recommendations on hepatitis c virus case-finding and access to care")

-Support for the implementation of the Welsh Government's policy initiative for community pharmacy-based hepatitis-c testing service, commissioned though WHC/2017/048.

-Knowledge exchange with policy makers, academics, practitioners and stakeholders engaged in the world-wide efforts to eliminate hepatitis C.

Concluding Comments

This thesis has aimed to present the case that decentralised care provided by non-specialists can enable more people infected with hepatitis C to access a cure, using the example of a pharmacist-led pathway. The research programme has utilised an iterative approach to developing and evaluating a complex intervention. The activities involved in the generation of research have aimed to develop the practice of pharmacy: a clinical profession.

CHAPTER 9

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CHAPTER 9

APPENDICES

9.1	A systematic review and meta-analysis of community and primary-care-based hepatitis C testing and treatment services that employ direct acting antiviral drug treatments
9.2	'Standing Outside the Junkie Door'—service users' experiences of using community pharmacies to access treatment for opioid dependency
9.3	Application of a discrete choice experiment approach to support the design of a hepatitis C testing service in primary care
9.4	A quasi-experimental evaluation of dried blood spot testing through community pharmacies in the Tayside region of Scotland
9.5	DOT-C: A cluster randomised feasibility trial evaluating directly observed anti-HCV therapy in a population receiving opioid substitute therapy from community pharmacy
9.6	Clinical effectiveness of pharmacy-led versus conventionally delivered antiviral treatment for hepatitis C in patients receiving opioid substitution therapy: a study protocol for a pragmatic cluster randomised trial
9.7	Clinical effectiveness of pharmacy-led versus conventionally delivered antiviral treatment for Hepatitis C in patients receiving opioid substitution therapy: A pragmatic cluster randomised trial
9.8	Using a systems-thinking approach to elucidate programme theory underpinning the effectiveness of the SuperDOT-C Intervention: a pharmacy-led test and treat pathway for PWID with hepatitis c infection prescribed opioid substitution therapy