Study Protocol

Evaluating Treatment as Prevention among People Who Inject Drugs in Dundee for HCV (E-raPiD-HCV)

Study Acronym	Erapid
Sponsor	University of Dundee and NHS Tayside
Sponsor R&D Number	2016GA08
Funder	Merck Sharp Dohme (MSD)
Chief Investigator	Professor John Dillon
REC Number	17/ES/0136
Clinical Trials Unit	Tayside Clinical Trials Unit (TCTU)
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Contents

Signatures

The undersigned confirm that the following protocol has been agreed and approved by the Sponsor and that the Chief Investigator agrees to conduct the trial/study/study in compliance with this approved protocol and will adhere to the principles of GCP, the Sponsor SOPs, and any other applicable regulatory requirements as may be amended from time to time.

John Dillon Chief Investigator	Signature	Date

LIST OF ABBREVIATIONS

CI	Chief Investigator
CNORIS	Clinical Negligence and Other Risks Scheme
HCV	Hepatitis C Virus
GCP	Good Clinical Practice
NESI	Needle exchange surveillance initiative
NSP	Needle service programme
OST	Opioid substitution therapy
PWID	People who inject drugs
REC	Research Ethics Committee
SOP	Standard Operating Procedures
SMF	Study Master File
SVR12	Sustained viral response at least 12 weeks after end of treatment
SMG	Management Group
TSC	Trial Steering Committee

SUMMARY/SYNOPSIS

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Study Title	**Evaluating Treatment as Prevention among People Who Inject Drugs in Dundee for HCV (E-raPiD-HCV)**	
Study Design	The aim of this study is to conduct an evaluation of hepatitis C treatments in NHS Tayside in order to empirically test the "treatment as prevention" models. This will be done by analysing the records of patients who have been tested and treated for hepatitis C using NHS Tayside databases. There will be no interventions carried out as part of this study.	
Study Population	This study will monitor the target PWID population (we estimate approximately 2,800 individuals) as we intensify the number of treatments provided to this population and achieve levels of treatment that will test the "treatment as prevention" concept.	
Sample Size	Approximately 2,800 individuals	
Planned study Period	6 years	
Primary	***Objectives*** To demonstrate treatment as prevention reduces HCV.	***Outcome Measures*** HCV testing in NHS Tayside
Secondary	***Objectives***	***Outcome Measures***
	To develop the analytic framework that can be used to assess the impact of treatment as prevention, incorporating evidence from multiple sources and taking into account uncertainty and bias	Numbers of patients engaged in treatment and SVR_{12} during the treatment phase
	To develop dynamic cost-effectiveness models of HCV treatment among PWID	Costs of treatment pathways and infection rates
	Re-infection with HCV following treatment	Annual routine offer of HCV testing
Inclusion Criteria	All individuals in NHS Tayside eligible for HCV testing and treatment according to Scottish Intercollegiate Guidelines Network guidelines.	
Exclusion Criteria	None	

1 INTRODUCTION

Hepatitis C is a blood-borne virus (HCV) that can seriously damage the liver and is spread mainly through blood-to-blood contact with an infected person. The “serious and significant public health risk” posed by HCV was recognised during a member’s debate in the Scottish Parliament in 2004. By December 2006, Health Protection Scotland estimated that 50,000 persons in Scotland had been infected with the Hepatitis C virus and that 38,000 were chronic carriers (1, 2). Currently, the greatest risk of acquiring the virus in the UK is through injecting drug use. In Scotland, it is estimated that over 85% of individuals who have Hepatitis C were infected in this way (3).

The outcome of HCV infection varies considerably between individuals. Some (up to 25%) are able to clear the infection spontaneously, whilst the remaining 75% become chronically infected (4). Within the subpopulation of chronically infected patients, some will develop serious liver disease, including cirrhosis and hepatocellular carcinoma, within a few years, whilst in others liver disease will not progress even over a period of more than forty years. Hepatitis C is often referred to as the ‘silent epidemic.’ Many who are infected are unaware of it, and often show no symptoms over a long period of time. While there is presently no vaccination for Hepatitis C, the recent introduction of protease inhibitor-based directly acting anti-viral treatments (DAA) has begun a new era in treatment of this disease (5). These new oral treatments are extremely safe, have shorter treatment regimens than previous drugs, and are effective, producing a cure in over 90% of cases providing compliance is adequate (6).

The advent of more effective DAA therapies raises the possibility of using therapy as prevention, turning the epidemic off at source, by targeting active infected drug users who are the main source of new infections.

Our modelling work shows that HCV treatment is a critical component to HCV prevention among people who inject drugs and is likely to be cost-effective compared to delaying treatment or treating non-PWID with mild or moderate disease (7-11). For example, we show in a number of settings with chronic HCV in PWID below 60% that treating 10-20 per 1000 drug users per year can reduce HCV prevalence by 50-90% over 10-15 years; that for every one PWID treated in the 20% chronic HCV setting 2 new HCV infections are averted. The scale of the benefit is inversely and exponentially related to prevalence of HCV in the population, the lower the prevalence the sooner and bigger the impact.

Current conventional treatment pathways focus on populations drawn from those known to drug problem services and former drug users. Treating people who are the most stable and with a low risk of relapse back into chaotic injecting will reduce future morbidity in the individual patients but may not achieve additional benefit in terms of averting future infections. Our recent work within Tayside has shown that we are able to test less stable, actively injecting drug users for Hepatitis C and then successfully treat them using both the conventional care pathway and non-conventional care pathways, such as needle exchange clinics (e.g. Eradicate study, completed February 2017; Advance study, started in January 2018, ongoing), community pharmacies (SuperDOTC study, December 2016 – January 2019. REACH HCV study, started February 2020, ongoing) and prisons (12). If the models are correct, this intensive treatment programme will effectively eradicate Hepatitis C from Tayside over the next few years. However, the models are not yet empirically tested and they make some assumptions that if violated may lead to over or under-estimation of the intervention effect. For example, the models assume that (a) heterogeneity in injecting risk and uptake of HCV testing and treatment will even out as PWID move and transition between high and low risk periods; and (b) that HCV transmission risk for susceptible PWID is similar for those that have achieved SVR or are untreated.

Our intensive treatment approach in Tayside provides an ideal opportunity to empirically test the “treatment as prevention” models. The current study will not involve direct recruitment or treatment of patients. Instead, it will evaluate the portfolio of care pathways currently being used to treat HCV in Tayside and test the hypothetical modelling to determine whether treatment of HCV will work as prevention of future spread of the virus.

2 BACKGROUND & RATIONALE

We have embarked on a series of studies that will dramatically increase the number of PWID with HCV infection who are being treated. This allows us to test empirically modelling data predicting treatment as prevention works for HCV infection. We are aiming to treat enough people actively injecting drugs who are infected with Hepatitis C in Tayside to reduce the prevalence in this population from approximately 29% to less than 10%. This will reduce the incidence of new infections from over 5% per annum to less than 1% per annum which we can detect with population surveillance techniques.

3 STUDY OBJECTIVES & OUTCOMES

Table 1: Primary Objectives and Outcome Measures

Primary Objective:	**Outcome Measure:**	**Timepoint of outcome measured**
To demonstrate treatment as prevention reduces HCV.	HCV testing in NHS Tayside	Annually

Table 2: Secondary Objectives and Outcome Measures

Secondary Objective:	**Outcome Measure:**	**Timepoint of outcome measured**
To develop the analytic framework that can be used to assess the impact of treatment as prevention, incorporating evidence from multiple sources and taking into account uncertainty and bias	Numbers of patients engaged in treatment and SVR_{12} during the treatment phase	Years 1-3
To develop dynamic cost-effectiveness models of HCV treatment among PWID	Costs of treatment pathways and infection rates	Year 5
Re-infection with HCV following treatment	Annual routine offer of HCV testing	Following treatment and subsequently annually for each PWID

4 STUDY DESIGN

4.1 INTERVENTION

There is no intervention associated with this study.

4.2 STUDY DESCRIPTION

The aim of this study is to conduct an evaluation of hepatitis C treatments in NHS Tayside in order to empirically test the “treatment as prevention” models. This will be done by analysing the records of patients who have been tested and treated for hepatitis C using NHS Tayside databases. Individuals working on this project will apply for Caldicott Guardian approval. As described previously, a number of strategies are being used to intensively identify and treat individuals with hepatitis C within Tayside.

4.3 STUDY FLOWCHART

There will be no interventions carried out as part of this study. The timepoints for measurements are shown in Table 2.

4.4 STUDY MATRIX

There will be no interventions carried out as part of this study. The timepoints for measurements are shown in Table 2.

4.8 INCIDENTAL FINDINGS

4.9 STUDY POPULATION

The entire PWID population in Tayside (we estimate approximately 2,800 individuals)

4.10 NUMBER OF PARTICIPANTS

Approximately 2,800 individuals

4.11 INCLUSION CRITERIA

Data will be included from NHS Tayside NESI and treatment databases so the inclusion criteria will be all those eligible for HCV testing and treatment in NHS Tayside.

Scottish Intercollegiate Guidelines Network (SIGN) guidelines recommend that the following groups should be offered testing :

- patients with an otherwise unexplained persistently elevated alanine aminotransferase
- people with a history of injecting drug use
- people who are human immunodeficiency virus (HIV) positive
- recipients of blood clotting factor concentrates prior to 1987
- recipients of blood and blood components before September 1991 and organ/tissue transplants in the UK before 1992
- children whose mother is known to be infected with HCV
- healthcare professionals following percutaneous or mucous membrane exposure to blood which is, or is suspected to be, infected with HCV
- people who have received medical or dental treatment in countries where HCV is common and infection control may be poor
- people who have had tattoos or body piercing in circumstances where infection control procedure is, or is suspected to be, suboptimal
- people who have had a sexual partner or household contact who is HCV infected.
- Anyone who believes themselves to be at risk.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Individual participants will not be consented into this trial. In accordance with the inclusion criteria, participants will be identified and analysed using NHS Tayside databases (following Caldicott approval).

6 DATA COLLECTION & MANAGEMENT

6.1 DATA COLLECTION

Details of all patients who are undergoing or have completed HCV treatment in Tayside are entered into a clinical database as per standard care by specialist HCV nurses and this practice will continue as we intensify treatment rates through our clinical trials and NHS treatment pathways. Data in this database will form the source for treatment initiation and outcomes. Twice a year the number of patients treated and cured since last data extraction will be extracted with no patient identifiable information but with data on viral genotype, stage of liver disease, pathway of treatment delivery and current drug use status.

Data on infection rates from routine HCV testing within NHS Tayside is also collected in the virology service in Tayside for government reporting. On a six monthly basis we will extract data on known HCV negative patients who have been retested in that time period. The data extraction will consist of the date when they were last known to be negative, the date of re-test and the result of the test. No patient identifiable data will be used.

Population level data will be collected 6 monthly around the anniversary of the study commencement or to coincide with the NESI data collection cycles.

The source data will be accessed by the clinical care team and clinical data which is not patient identifiable entered into the study data management system which will be built within Excel and held on a University server that is GCP compliant; regularly backed-up, has access controls and updates to operating system and security software. Caldicott approvals will be obtained as required.

6.2 DATA MANAGEMENT SYSTEM

Data management will be conducted in compliance with TASC SOPs on Data Management, including TASC SOP33 Data Management to GCP standards and TASC SOP53 Data Management Systems in Clinical Research.

The data management system (DMS) will be Excel. The data will be used to calculate the treatment rate and cure rate for the time period and the rate of new infection. The core data will then be destroyed. The anonymized dataset may be shared with colleagues in other UK Universities.The database is managed in line with all applicable principles of medical confidentiality and UK law on data protection, namely, the Data Protection Act 1998, which brought UK law into line with the EU Data Protection Directive. The Data Controller will be the University of Dundee and the Data Custodian will be the CI.

7 STATISTICS AND DATA ANALYSIS

7.1 SAMPLE SIZE CALCULATION

All those eligible for HCV testing and treatment in Tayside, currently estimated at 2800.

7.2 PROPOSED ANALYSES

Initially descriptive analysis will be used. In the final analysis statistical and mathematical models will develop the analytic framework that can be used to assess impact incorporating evidence from multiple sources and taking into account uncertainty and bias from our multiple data sources. We will combine Multiple Parameter Evidence Synthesis and Infectious Disease Models in order to measure the primary outcome and objective. We also will establish what ongoing surveillance and monitoring arrangements are required in future evaluations, and project impact of interventions in other settings. In addition a vital output from the data will be an economic evaluation using dynamic cost-effectiveness models of HCV treatment among PWID. These models can inform other areas and treatment scenarios.
8.3

7.3 TRANSFER OF DATA

No patient identifiable data will be transferred from NHS Tayside.

8 STUDY MANAGEMENT AND OVERSIGHT ARRANGEMENTS

8.1 STUDY MANAGEMENT GROUP

The study will be co-ordinated by a Management Group, consisting of the grant holder (CI), Study Manager, and research fellow.

8.2 STUDY STEERING COMMITTEE

A Study Steering Committee (SC) will not be established for this study. The Erapidstudy will eventually form a part of a larger study with more sites (Epitope). This larger study will compare the measures of HCV incidence in NHS Tayside, collected as part of the Erapid study, with similar measures in other regions of the UK where intensive treatment regimes for HCV infection are not currently carried out. A steering group will be established to oversee the conduct and progress of this larger study, which will include Erapid.

8.3 INSPECTION OF RECORDS

The CI will permit study related monitoring, audits, and REC review. The CI agrees to allow the Sponsor or, representatives of the Sponsor, direct access to all study records and source documentation.

9 GOOD CLINICAL PRACTICE

9.1 ETHICAL CONDUCT OF THE STUDY

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

In addition to Sponsorship approval, a favorable ethical opinion will be obtained from the appropriate REC and appropriate NHS R&D approval will be obtained prior to commencement of the study.

9.2 CONFIDENTIALITY

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.

9.3 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.

9.4 INSURANCE AND INDEMNITY

The University of Dundee and Tayside Health Board are Co-Sponsoring the study.

Insurance –The University of Dundee will obtain and hold a policy of Public Liability Insurance for legal liabilities arising from the study.

Tayside Health Board will maintain its membership of the Clinical Negligence and Other Risks Insurance Scheme ("CNORIS") which covers the legal liability of Tayside in relation to the study.

Where the study involves University of Dundee staff undertaking clinical research on NHS patients, such staff will hold honorary contracts with Tayside Health Board which means they will have cover under Tayside's membership of the CNORIS scheme.

Indemnity Co-Sponsors do not provide study participants with indemnity in relation to participation in the Study but have insurance for legal liability as described above.

10 ADVERSE EVENTS - NOT RELEVANT TO THIS STUDY

11 ANNUAL REPORTING REQUIREMENTS

Annual reporting will be conducted in compliance with TASC SOP 15: Preparing and Submitting Progress and Safety Reports in CTIMPs and Non-CTIMPs, as a condition of sponsorship and as a condition of a favourable opinion from a REC. An HRA Annual Progress Report for NCTIMPs will be prepared and submitted by the CI to REC, and copied to the Sponsor, on the anniversary date of the REC favourable opinion.

12 STUDY CONDUCT RESPONSIBILITIES

12.1 PROTOCOL AMENDMENTS, DEVIATIONS AND BREACHES

The CI will seek approval for any amendments to the Protocol or other study documents from the Sponsor, REC and NHS R&D Office. Amendments to the protocol or other study docs will not be implemented without these approvals.

In the event that a CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the CRF, documented and submitted to the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and NHS R&D Office for review and approval.

In the event that a serious breach of GCP or protocol is suspected, this will be reported to the Sponsor Governance Office immediately

12.2 STUDY RECORD RETENTION

Archiving of study documents will be for five years after the end of study

12.3 END OF STUDY

The end of study is defined as database lock. The Sponsor or CI have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the Sponsor and REC within 90 days, or 15 days if the study is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

A summary report of the study will be provided to the Sponsor and REC within 1 year of the end of the study.

13 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

13.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team and the University of Dundee. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared.

13.2 PUBLICATION

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

13.3 PEER REVIEW

14 REFERENCES

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7. Martin NK, Vickerman P, Foster GR, Hutchinson SJ, Goldberg DJ, Hickman M. Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility. J Hepatol. 2011 Jun;54(6):1137-44.
8. Innes H, Goldberg D, Dillon J, Hutchinson SJ. Strategies for the treatment of Hepatitis C in an era of interferon-free therapies: what public health outcomes do we value most? Gut. 2015 Nov;64(11):1800-9.
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