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A RANDOMISED CONTROLLED TRIAL OF ACTIVE CASE MANAGEMENT TO LINK HEPATITIS C NOTIFICATIONS TO TREATMENT IN TASMANIA, AUSTRALIA – A STUDY PROTOCOL

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Abstract

Introduction

By subsidising access to direct acting antivirals (DAAs) for all people living with hepatitis C (HCV) in 2016, Australia is positioned to eliminate HCV as a public health threat. However, uptake of DAAs has declined over recent years and new initiatives are needed to engage people living with HCV in care. Active follow up of HCV notifications by the health department to the notifying general practitioner (GP) may increase treatment uptake, and is the primary aim of this trial.

Methods and analysis

This study is a randomised controlled trial comparing enhanced case management of HCV notifications with standard of care. The intervention includes phone calls from a department of health (DoH) specialist HCV nurse to notifying GPs and offering HCV management support. The level of support requested by the GP was graded in complexity: level one: HCV information only; level two: follow up testing advice; level three: prescription support including linkage to specialist clinicians; and level four: direct patient contact. The study population includes all GPs in Tasmania who notified HCV diagnosis to the DoH between September 2020 and December 2021.

The primary outcome is proportion of HCV cases who initiate DAAs after 12 weeks of HCV notification to the health department. Secondary outcomes are proportion of HCV notifications that complete HCV RNA testing, treatment work-up, and treatment completion. Multiple logistic regression modelling will explore factors associated with the primary and secondary outcomes. The sample size required to detect a significant difference for the primary outcome is 85 GPs in each arm with a two-sided alpha of 0.05 and 80% power.

Ethics and dissemination

The study was approved by University of Tasmania's Human Research Ethics Committee (Protocol ID: 18418) on 17 December 2019. Results of the project will be presented in scientific meetings and published in peer-reviewed journals.

Registration details

The trial is registered on ClinicalTrials.gov (ID: NCT04510246)

Trial progression

The study commenced recruitment in September 2020

STRENGTHS AND LIMITATIONS

- With DAA treatment numbers falling in Australia, despite easy access and publicly subsidised treatment, new approaches are needed to engage providers and people diagnosed with HCV in care.
- This is the first randomised study utilising complete jurisdictional disease notifications data to determine effectiveness of supporting linkage to care and treatment for all people prospectively notified with hepatitis C infection.
- This trial is examining the effectiveness of guiding care pathways for prospectively notified diagnoses, but additional challenges exist for using historical notifications to reengage people previously diagnosed with HCV in care.
- There is a risk of contamination of the intervention if GPs at the same clinic are randomised to different arms of the study, which might under-estimate the true benefit.
- The study runs a risk of high loss to follow up particularly with locum GPs as they move across practices.

Introduction

Hepatitis C virus (HCV) affects approximately 71 million people globally causing 400,000 deaths each year [1]. In Australia, approximately 180,000 people were estimated to be living with HCV in 2017 [2]. The availability of direct-acting antiviral medications (DAAs) on the Pharmaceutical Benefits Scheme (PBS) since March 2016, has revolutionised HCV care[3]. The simplicity and tolerability of these new treatments, combined with Australia providing largely unrestricted access to DAAs in primary care, makes it possible for Australia to eliminate HCV as a public health threat [4, 5].

To realise this once-in-a-generation opportunity, it is imperative that sufficient numbers of people complete treatment in order to interrupt transmission [5]. While in the initial year of DAA subsidy in 2016 over 32,000 treatments were prescribed, the number of people commencing treatment has declined considerably; in 2019, 11,580 DAA treatments were prescribed [6], below the estimated 13,680 annual treatments needed to achieve HCV elimination in Australia by 2030 [7]. As such, initiatives are needed to actively engage people living with hepatitis C in care and ensure that health care providers are appropriately equipped to prescribe DAAs or link patients to treatment.

DAAs can be prescribed by general practitioners (GPs) in Australia. The proportion of Australians receiving DAA treatment via their GP increased from 8% at the introduction of DAAs in March 2016 to 40% in May 2017, but has remained stable since [6]. There are clear guidelines available for hepatitis C treatment, and the introduction of pan-genotypic regimens in August 2017 has further simplified treatment options [3]. However, DAA access barriers remain, particularly for people who inject drugs who are a key group for hepatitis C elimination efforts [5]. Qualitative research amongst both consumers and providers of health care has suggested that a lack of provider follow-up and support is a barrier to treatment uptake after diagnosis [8-10].

Hepatitis C is a notifiable disease in Australia and notifications represent an opportunity to link patients to treatment. Consistent with other Australian jurisdictions, in Tasmania, the setting for this study, laboratories conducting hepatitis C testing notify positive hepatitis C test results to the Department of Health (DoH) [11] in accordance with Communicable Disease Network of Australia Hepatitis C surveillance case definition [12]. This study is the first randomised controlled trial to assess the impact of active case follow-up of hepatitis C notifications using a jurisdiction-wide disease notifications system to support linkage to care and treatment. This study designates a DoH specialist HCV nurse embedded within the Tasmanian DoH to contact GPs and provide supported assistance after a hepatitis C diagnosis is notified. The study will evaluate whether active follow up of providers with enhanced case management is more effective in enhancing uptake of hepatitis C treatment compared to current standard of care for new notifications by the DoH. The study will also compare the cost-effectiveness of the enhanced case management compared to current standard of care for positive hepatitis C antibody notifications.

Methods and analysis

This study is a two-arm, cluster randomised controlled trial with randomisation at the level of the GP who notifies the DoH of a hepatitis C antibody positive case.

Study Setting

The study will be conducted in the Australian state of Tasmania with a population of approximately 530,000 [13] and an estimated 3,349 people living with hepatitis C [2]. The preceding ten years have seen an average 260 new hepatitis C notifications in Tasmania annually, with a new notification rate of 48.6 per 100,000 population, slightly higher than the national average of 43.3 per 100,000

population [2]. The entire state will be included in the trial, as all notifications are received and managed by a central body at the Tasmanian DoH.

Participant Eligibility

All GPs who have requested a hepatitis C antibody test that leads to new or repeat notification to the Tasmanian DoH will be eligible for participation in this study. Notifications of new positive hepatitis C antibody tests are made by the laboratory conducting the test.

Randomisation and Allocation

The unit of randomisation is at the GP level and will be done within 3 weeks of HCV notification receipt by the DoH and by the order they are received. GPs will be allocated one-to-one at their first notified case during the follow-up period and all subsequent notifications will receive either standard or care or intervention arm case management consistent with the initial randomisation. This will ensure that standard of care and intervention arms are not cross-contaminated by GPs that make multiple notifications. The sequence will be performed using the randomisation function within REDCap. A representation of randomisation and the study process and activities in each arm is shown in Figure 1.

Blinding

Given the nature of the intervention, it is impossible to blind either the DoH specialist HCV nurse or the GP to allocation. Analyses will be independently conducted by analyst statistician at the Burnet Institute who will be blinded to intervention allocation.

Description of Intervention

Standard of care arm:

When a laboratory in Tasmania has a positive hepatitis C antibody test result, they formally notify this case to the DoH. A 'hepatitis C notification' requires laboratory definitive evidence of a positive hepatitis C antibody test or hepatitis C RNA test in a person with no prior evidence of hepatitis C virus infection [12]. Notifications can be further classified by DoH as 'newly-acquired', which is defined by laboratory or clinical evidence that infection occurred within the preceding 24 months [14], and notifications where a person has prior evidence of hepatitis C infection are classified as a 'repeat' notification. Under the Communicable Diseases Network Australia (CDNA) case definitions, 'unspecified' hepatitis C is a confirmed case that is not notifiable, similar to 'repeat' notifications [15]. At present, repeat notifications receive no further follow up by the DoH. In this protocol, the term 'new' notification is used to indicate all notifications that meet the case definition (regardless of whether they are 'newly-acquired' or not), and use the term 'repeat' notifications if the patient has prior evidence of hepatitis C virus infection.

After receipt of a hepatitis C notification, surveillance officers check the details of the case to determine whether the test represents a new or repeat notification. For cases determined to represent a 'new' notification, a request for further details of the case is mailed to the medical practitioner who requested the test. A routine surveillance letter and an enhanced surveillance data collection form are mailed to the GP. The aim of this request is to accurately capture surveillance data that pertains to testing history and risk factors. Advice on how to manage hepatitis C is also included in the routine surveillance letter. On assessment of returned enhanced surveillance data

collection form, the DoH may undertake further risk assessment, investigation and response activities. If the practitioner does not return the enhanced surveillance data collection form within 20 days, the form is re-posted to the practitioner. If cases are determined to be a repeat notification the current standard of care is to conduct no further activities regarding this case. Other jurisdictions around Australia follow a similar algorithm and process for managing new notifications.

Evaluation follow up

All GPs randomised to the standard of care arm will be contacted by telephone 12 weeks after the HCV notification date (see figure 1). Two weeks prior to the evaluation phone call, a study information letter (Supplementary material, Appendix A) will be sent to the GP. This is not current standard practise but will be performed by the DoH specialist HCV nurse for the project outcome evaluation. During this phone call consent will be sought for the GP to provide information about their clinical management of the notified patient. Details provided or missing from the standard enhanced surveillance data collection form would be confirmed with the GP at this phone call. Three attempts to contact the practitioner will be made within a 30-days of receipt of the hepatitis C notification before they are classified as lost to follow-up.

Intervention Arm

GPs randomised to the intervention arm will receive the standard of care surveillance letter, enhanced surveillance data collection form for new hepatitis C notifications, and a study information letter (Supplementary material, Appendix A). In addition to standard of care procedures, all notifications (new and repeat) will be offered further enhanced case management support by a DoH specialist HCV nurse. Support is offered at the initial phone call, and is made available over a 12-week period during which the DoH specialist HCV nurse can do follow-up calls with the GP or directly with the patient.

Initial phone call

Within 3 weeks of the HCV notification being received by the DoH, GPs randomised to the intervention arm will receive an initial phone call from the DoH specialist HCV nurse. During this call, GPs are consented into the study and offered enhanced case management support in line with approved guidelines for hepatitis C management [3]. Three attempts will be made to contact the practitioner within a 30-day period before they are classified as lost to follow-up.

The DoH specialist HCV nurse will initially confirm the notification made by the with GP and ask if the: 1) patient had been recalled for further management; 2) whether a hepatitis C RNA test has been ordered; and 3) of any RNA positive patient, whether treatment options had been discussed, offered or initiated. A tailored level of enhanced case management support is then offered depending on RNA status, GPs needs, and familiarity with HCV prescribing (Model 1), and support needed for their patient (Model 2).

Enhanced case management support for GP (Model 1)

Level 0: No assistance required, GP already confident in managing HCV treatment
Level 1: General information on hepatitis C care and treatment
Level 2: Further diagnostic testing advice and support to conduct pre-treatment work-up assessment
Level 3: DAA prescription guidelines including that treatment can be prescribed by the GP and when/how to refer for specialist care.

- Advising on conducting post-cure management including methods of follow-up to manage risks; including harm minimization, reducing re-infection risk, opioid substitution therapy

- Linking/referral to resources for patients with cirrhosis or other concerns to specialist support for ongoing management

The GP may indicate the preference to receive the enhanced case management support via several phone calls or emails.

Enhanced case management for patient (Model 2)

Level 4: Direct patient contact

The GP will also be offered the option of the DoH specialist HCV nurse contacting the patient directly with their consent to notify them of their result and inform them about further testing and treatment options and referral back to their GP or other primary care or specialist. Model 2 is an option for GPs at any level of support in Model 1.

Evaluation follow up

As with the standard of care arm, GPs in the intervention arm will be contacted by telephone call 12 weeks after an HCV notification date to complete the details of the patient outcomes for the specific case. Details provided or missing from the standard DoH enhanced surveillance data collection form will be confirmed with the GP at this phone call (see figure 1). Similar to the standard of care arm, three call attempts will be made to contact the practitioner within a 30-day period prior to classifying the GP as lost to follow-up.

Outcomes

Primary outcome

The primary outcome is the proportion of cases notified with hepatitis C who commence hepatitis C treatment within 12 weeks of HCV notification as evidenced by confirmation from the GP. This will be assessed using the information provided by GPs at the evaluation phone call and will be compared across the two arms and the model and level of support offered.

Secondary outcomes

At the evaluation phone call for both the standard of care and intervention arm, additional outcome measures will be collected which we will collate into:

- Proportion of people diagnosed with hepatitis C antibody with a documented HCV RNA test result;
- Proportion of people diagnosed with hepatitis C (HCV RNA+) completing treatment work-up blood tests;
- Proportion of people diagnosed with hepatitis C (HCV RNA+) completing an appropriate course of hepatitis C treatment as prescribed.

To evaluate patient-factors that may have an impact on the likelihood of people commencing hepatitis C treatment, the project will utilise de-identified aggregated data from the DoH obtained through the standard surveillance procedures in determining risk exposures, age, gender and date of diagnosis. The likelihood of commencing support will also be evaluated by model and level of support and number and types of contacts made.

Data Collection

The first data point collection will be completed by the DoH specialist HCV nurse when conducting the initial telephone call to the GPs in the intervention arm to confirm eligibility and consent (Supplementary material, Appendix B). No identifying patient details will be recorded for the evaluation of the project: any clinical information that the DoH specialist HCV nurse and the GP discuss for clinical management of individuals is not collected for the purpose of this project. Data collected from participating GPs will be allocated a study identification (ID) and a patient ID for the case with HCV (Supplementary material, Appendix C).

The second format of data collection will concurrently record the nature of the activities (level of support, HCV notification details) and time taken to complete them by the DoH specialist HCV nurse as part of the hepatitis C management assistance provided to the practitioner. This will be recorded in an excel spreadsheet, using the numerical participant's/GP 's study ID (Supplementary material, Appendix D). This information will enable determination of the costs of the intervention, to inform cost-effectiveness estimates. No identifying patient details will be sought or recorded for the purpose of the evaluation of the project.

The DoH specialist HCV nurse will collate de-identified information for the purpose of the evaluation of the project from the participant/GP of the outcome of HCV care of the notifications. Also, from the DoH standard enhanced surveillance data collection form, any missing data will be collected for standard of care purposes; e.g. dates of testing, the patient's age, gender and risk exposures. For the purpose of the project, de-identified data will be collated from this form for the purpose of the project evaluation. These data will be extracted and stored with a unique patient study number.

Linkage between the patient ID and the GP's study ID will permit evaluation at service provider level which will maintain confidentiality of the participants/GP and patient data.

Data Management

The data from the phone surveys will be collected using REDCap software, and stored in a secure, password protected server at the Burnet Institute. It will be accessible to the DoH specialist HCV nurse, the study coordinator, data analysts at the Burnet Institute and the Institute's data manager. This data will be stored with a unique numerical GP study ID and patient ID.

All data entry will be performed by the DoH specialist HCV nurse based at Tasmanian DoH. A Burnet Institute researcher will check the data quality every month and liaise with the DoH specialist HCV nurse if there are any errors or inconsistencies.

The participant/GP log (Supplementary material, Appendix D) and record of activities and time spent will be kept on a password protected server accessible only to the DoH specialist HCV nurse and study investigators at the Tasmanian Department of Health.

Data will be monitored by a Burnet Institute staff member reviewing the collected data monthly to identify any errors or inconsistencies. Any issues or uncertainties will be followed up with the DoH specialist HCV nurse to clarify meaning of data and ensure robust entry processes.

Statistical Analysis

Sample size

Data supplied by the Tasmanian DoH indicate that in the period from January 2018 to November 2018, taking both repeat and new notifications combined, 274 GPs notified at least one case of hepatitis C; 174 had notified one case, 65 had notified two cases, 14 had notified three cases, and 21 had notified

four or more cases. On this basis, an estimated 224 GPs were expected to notify at least one case of hepatitis C during the 9-month study recruitment period.

The sample size required for a parallel design comparing HCV treatment uptake in the standard of care arm of **8%** and **25%** in the intervention arm is 85 GPs in each study arm with a two-sided alpha of 0.05 and 80% power (see Supplementary material, Appendix E). To account for measured correlation between different notifications clustered within the same GP, we used an intra-class correlation coefficient (ICC) of 0.10. Existing data estimates between 3-8% of people start therapy within three months (when our primary outcome will be assessed): data on national treatment uptake by specialists and general practitioners,[16] among people who inject drugs,[17] and in traditional referral to outpatient services all estimate treatment uptake of 8% or under at three months.[18] In this study, we will assume the higher (and therefore more conservative, biasing towards the null hypothesis) estimate of treatment uptake of 8% at three months in the standard of care arm. Treatment uptake in intervention arm is estimated at 25% based on best estimates of intervention acceptance by GPs and follow up, RNA prevalence among those notified with HCV antibody, community treatment eligibility, and best estimate of intervention effect [19-21]. Based on the estimates of 224 unique GPs notifying hepatitis C cases in a 9-month period, there is ample power to detect significant difference between arms even with the presence of clustering of notifications within clinicians.

Analysis of primary outcome

The primary analysis will be assessed as a binary outcome comparing the proportion of patients who commenced treatment in an intention to treat analysis in the Intervention arm compared to the Standard of Care arm.

Analysis of secondary outcomes

Other secondary outcomes will be analysed using the same intention to treat method. A per protocol analysis is proposed.

Multiple logistic regression modelling will explore factors predicting success of aspects of the cascade of care based on information obtained through the notification system, as well as information on the practitioner, associated with the primary and secondary outcomes. Factors to be explored in the multiple regression model include patient sociodemographic, GP's HCV care experience, number of notifications per practitioner, and time taken to reach GP/patient post HCV notification.

There will be no interim analysis or stopping guidelines.

Subsequent research following study completion

Data collection will permit future economic evaluation and cost-effectiveness modelling. Subject to further ethics review, consent may also be sought to contact participants/GPs later to assess rates of treatment success (sustained virological response) amongst notified cases who received treatment.

Ethics and dissemination

The study was approved by the University of Tasmania's Human Research Ethics Committee (Protocol ID: 18418) on 17 December 2019. GPs in either the Standard of Care arm or in the

Intervention arm will be contacted by the DoH specialist HCV nurse will contact the GP by phone, provide an explanation of the study and if the practitioner is interested in participating, verbal consent will be obtained. The project will also use surveillance data collected by the DoH for hepatitis C notifications. The researchers are requested a waiver of consent for the use of the data as it is an existing methods of public health program surveillance.

The results of the project will be presented in scientific meetings and published in peer-reviewed journals. Publication of data derived from the study will be supervised by the Protocol Steering Committee. All published quantitative data will be non-identifiable grouped data, none of which will be specific to a participant/GP. A plain English summary of study outcomes, as well as abstracts from publications, will be available on the Burnet Institute website. Authorship for publications arising from this study will adhere to the International Committee of Medical Journal Editors guidelines [22].

Patient and public involvement

There was no direct patient and public involvement in this protocol development. However, a qualitative exploration of the acceptability of hepatitis C notification systems study conducted with key informants including those with hepatitis C lived experience informed the study intervention [23].

Trial progress

The study commenced enrolments in September 2020.

References

1. Global hepatitis report 2017. Geneva: World Health Organization; 2017.
2. Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia: annual surveillance report 2018. Sydney: Kirby Institute; 2018.
3. Hepatitis C Virus Infection Consensus Statement Working Group. Australian recommendations for the management of hepatitis C virus infection: a consensus statement (September 2018). Melbourne: Gastroengerological Society of Australia; 2018.
4. Pedrana AE, Sacks-Davis R, Doyle JS, Hellard ME. Pathways to the elimination of hepatitis C: prioritising access for all. Expert Rev Clin Pharmacol. 2017;10(10):1023-6.
5. Scott N, Doyle JS, Wilson DP, Wade A, Howell J, Pedrana A, et al. Reaching hepatitis C virus elimination targets requires health system interventions to enhance the care cascade. Int J Drug Policy. 2017;47:107-16.
6. The Kirby Institute. Monitoring hepatitis C treatment uptake in Australia (Issue 9, July 2018). Sydney: Kirby Institute; 2018.
7. Scott N, Sacks-Davis R, Wade AJ, Stoove M, Pedrana A, Doyle JS, et al. Australia needs to increase testing to achieve hepatitis C elimination. Medical Journal of Australia. 2020;212(8):365-70.
8. Madden A, Hopwood M, Neale J, Treloar C. Beyond interferon side effects: What residual barriers exist to DAA hepatitis C treatment for people who inject drugs? PLoS One. 2018;13(11):e0207226.
9. Skeer MR, Ladin K, Wilkins LE, Landy DM, Stopka TJ. 'Hep C's like the common cold': understanding barriers along the HCV care continuum among young people who inject drugs. Drug Alcohol Depend. 2018;190:246-54.
10. Richmond JA, Wallace J. Implementation of hepatitis C cure in Australia: one year on. J Virus Erad. 2018;4(2):115-7.
11. The Director of Public Health. Guidelines for Notifying Diseases and Food Contaminants. In: Public Health Services TG, Department of Health and Human Services, editor. Tasmania: Tasmanian Government; 2016.
12. Communicable Disease Network Australia. Hepatitis C (unspecified) case definition Canberra: Australian Government Department of Health; 2004 [updated 12th March 200420th February 2019]. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_hepcun.htm.
13. Tasmanian Government Economic Analysis Unit. Population (ABS Cat No 3101.0). Hobart: Department of Treasury and Finance, Tasmanian Government; 2018.
14. Communicable Disease Network Australia. Hepatitis C (newly acquired) case definition Canberra: Australian Government Department of health; 2015 [updated 25th September 201520th February 2019]. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_hepcnew.htm.
15. Communicable Diseases Network Australia. Australian national notifiable diseases and case definitions: CDNA; 2004 [Available from: https://www1.health.gov.au/internet/main/publishing.nsf/Content/cdna-casedefinitions.htm.
16. Doyle JS, Scott N, Sacks-Davis R, Pedrana AE, Thompson AJ, Hellard ME. Treatment access is only the first step to hepatitis C elimination: experience of universal anti-viral treatment access in Australia. Alimentary pharmacology & therapeutics. 2019;49(9):1223-9.
17. Iversen J, Grebely J, Catlett B, Cunningham P, Dore GJ, Maher L. Estimating the cascade of hepatitis C testing, care and treatment among people who inject drugs in Australia. International Journal of Drug Policy. 2017;47:77-85.
18. Wade A, MacDonald DM, Doyle JS, Gordon A, Roberts S, Thompson AJ, et al. The cascade of care for an Australian community-based hepatitis C treatment service. PloS one. 2015;10(e0142770).

19. Burnet Institute and Kirby Institute. Australia's progress towards hepatitis C elimination - Annual Report 2020. Melbourne: Burnet Institute; 2020.
20. Von Bibra S, Doyle JS, Higgs P, Dietze PM, Desmond P, Stoove M, et al. Feasibilty of recruiting people who inject drugs into a nurse-led model of care trial: The TAP study. J Hepatol. 2016;62(2):S817-S8.
21. Doyle JS, Santen DKv, Iser D, Sasadeusz J, O'Reilly M, Harney B, et al. Hepatitis C elimination by enhancing care and treatment among HIV co-infected individuals (the co-EC study): Real world evidence of decreasing HCV incidence and prevalence. J Hepatol. 2019;70:e329.
22. International Committee of Medical Journal Editors. Defining the role of authors and contributors: International Committee of Medical Journal Editors; 2019 [cited 2019 14th February 2019]. Available from: http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html.
23. Walker S, Wallace J, Latham N, Saich F, Pedrana A, Hellard M, et al. "It's time!": A qualitative exploration of the acceptability of hepatitis C notification systems to help eliminate hepatitis C. International Journal of Drug Policy. 2021;97.

Authors' contributions

JSD, MS, MHH, AP, VW, and AT were involved in the development of the initial idea, methodological design, and drafting the trial protocol for ethics. TM, JSD, and MS prepared the initial protocol manuscript and KPM, JR, KT, SM, FHJ, NS, DI, MV, and TS reviewed and edited the manuscript. TS is the trial statistician. KM is responsible for data collection and TM is the study coordinator. All authors reviewed and approved the manuscript.

Funding statement

This study is funded by AbbVie as an investigator initiated trial. The study funder will have no role in the study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

Competing interests statement

JD, MS and MH report investigator-initiated research funding to their institution from Gilead Science, AbbVie and Merck. JD reports honoraria for speaking to his institution from Gilead Sciences and AbbVie and MS reports consultant fees from Gilead Sciences. AP has received investigator-initiated grant funding from Gilead Sciences, MSD and Abbvie and speaker fees from Gilead Sciences for unrelated work.

Figure legend

Figure 1: Flowchart of study activities

Green coloured boxes indicated the critical time points in the study. Blue boxes indicate the intervention activities and the evaluation phone call which is made in both study arms.

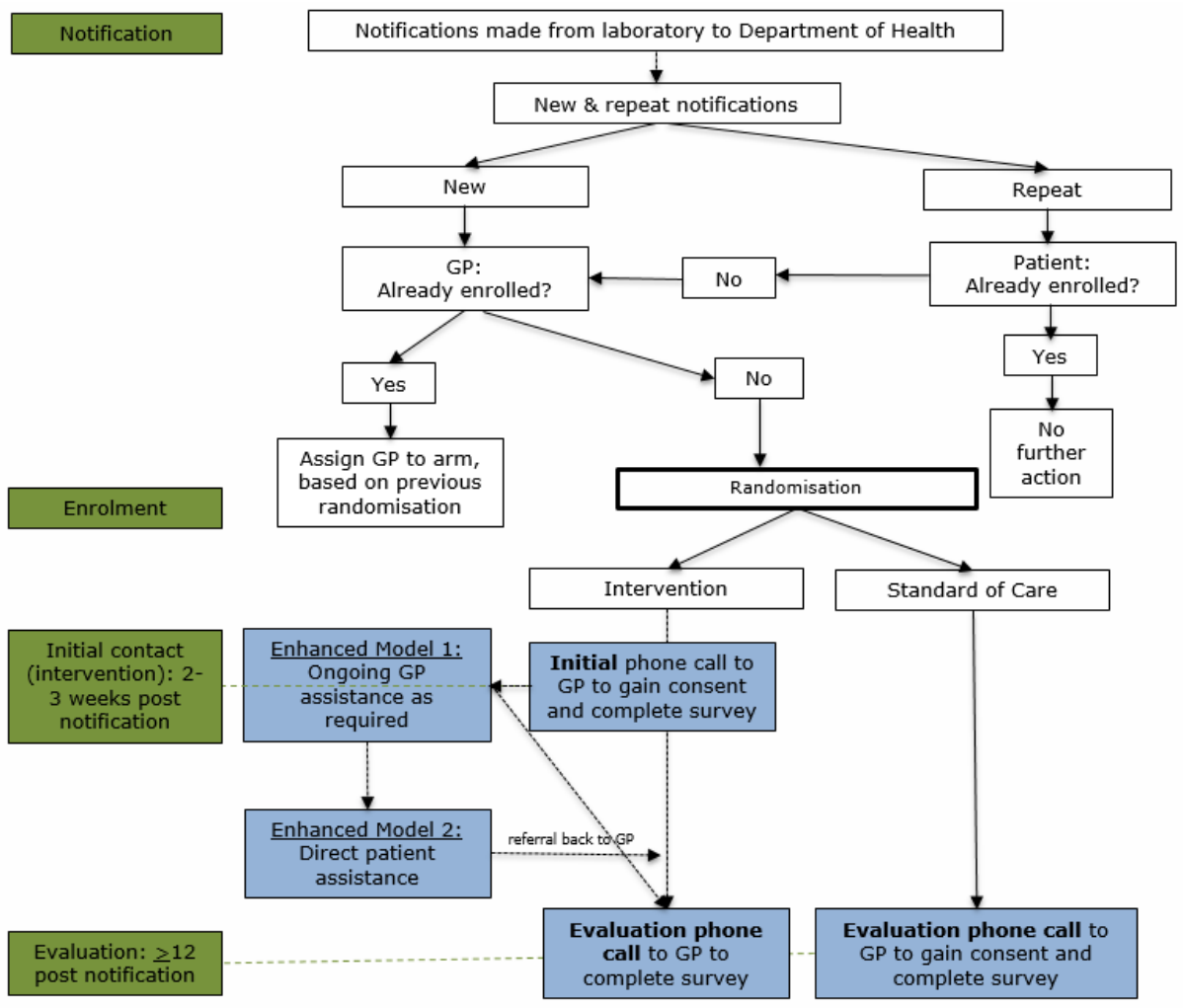

Figure 1: Flowchart of study activities

Green coloured boxes indicate the critical time points in the study. Blue boxes indicate the intervention activities and the evaluation phone call which is made in both study arms.

Supplementary information

Appendix A: Study Information Letter

Rachel Barter | Clinical Nurse Consultant Hepatitis C Research
Public Health Services| Department of Health
Ph: 6166 0634 | Fax: (03) 6173 0821 | Email: Rachel.Barter@health.tas.gov.au

«Title» «GP_First_Name» «GP_Last_Name»
«GP_Location»
«GP_Business_Address»
«City» «State» «Post_Code»

«Date»

Dear «Title» «GP_Last_Name»,

Re: Pilot project of active hepatitis C case management for new notifications in Tasmania

The simplicity of new treatments for hepatitis C make it possible for Australia to become one of the first countries to eliminate hepatitis C. **Despite the new treatments becoming available on the Pharmaceutical Benefits Scheme in 2016, half of Australians living with hepatitis C remain untreated[1].**

In accordance with Guidelines under the *Public Health Act 1997*, hepatitis C is a notifiable condition to the Director of Public Health. Public Health Services (Department of Health (DoH), Tasmania) and the Burnet Institute (Melbourne) are conducting a pilot project to determine if a new model of engaging General Practitioners (GPs) who provide care for diagnosed patients will increase treatment uptake (University of Tasmania HREC H0018418).

The project compares current DoH processes following a notification of hepatitis C (standard of care) with active engagement of GPs to provide enhanced case management (new model of care). All GPs in Tasmania who have diagnosed hepatitis C during the study period will be eligible to participate in the project and will be randomly assigned to either the new or standard model of care. This new model will be delivered by a DoH Clinical Nurse Consultant (CNC) who will contact the diagnosing doctor by phone and provide support, as needed, to facilitate hepatitis C pre-treatment testing, treatment, and post-curative support. The Clinical Nurse Consultant will also offer direct patient contact if requested by the GP. A follow-up evaluation phone call will be made to all participating GPs twelve weeks after the initial hepatitis C notification to assess whether enhanced case management results in increased uptake of hepatitis c treatment.

DoH records indicate that you recently requested testing that has resulted in a hepatitis C notification and you have been randomised to participate in the **new model/standard model of care.**

Our CNC Rachel Barter will contact you soon to invite you to participate in this project which we hope you will consider. Verbal consent will be sought on initial phone contact by Rachel. Your involvement will contribute to

[1] Burnet Institute and Kirby Institute. Australia's progress towards hepatitis C elimination: annual report 2019. Melbourne: Burnet Institute; 2019.

a rigorous evidence base for future practice, improve the opportunity for Tasmanians living with hepatitis C to be cured and assist us achieve our hepatitis C elimination goal.

If you wish to talk to Rachel Barter beforehand, please contact her on 6166 0634 or rachel.barter@health.tas.gov.au.

Yours sincerely,

Dr. Mark Veitch
Director, Public Health
Tasmanian Director of Public Health

Dr. Joseph Doyle MPH PhD FRACP FAFPHM
Infectious Diseases Physician
Deputy Director, Disease Elimination Program
Burnet Institute

Appendix B: GP questionnaire

This is the GP Form which will collect data on the GP and will randomise the GP using the REDCap tool online. This needs to be filled in only once for every GP.

A randomised controlled trial of active case management to link hepatitis C notifications to hepatitis C treatment in Tasmania

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GP Form

GP ID (REDCap assigned)	_____
GP ID_TNDD (as assigned by TNDD)	_____
Name of GP	_____
What is the postcode of the clinic where this GP works?	_____
Alternative postcode	_____

Please provide some information for GP ID [record_id]

Please confirm that all eligibility criteria for GP have been met	◯ Yes ◯ No
Group to which GP has been randomised	◯ Standard of Care ◯ Intervention
Has GP been reached yet?	◯ Yes ◯ No
Please confirm that GP consents to participate in the study	◯ Yes ◯ No
Please close this form and do not use this GP ID anymore.	
Please provide reason why GP is not willing to consent	◯ Time constraints ◯ Privacy issues ◯ Know enough about HCV ◯ Patient already referred to a specialist ◯ Patient no longer attends practice, transferred ◯ Patient is lost to follow up ◯ Declined to give a reason ◯ Other
Please specify 'other'	_____
Does GP have previous experience in HCV care?	◯ Yes ◯ No
Have you ever written a DAA script?	◯ Yes ◯ No

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Please close this form and do not use this GP ID anymore.	
Has the GP been reached at the 12 week evaluation phone call?	◯ Yes ◯ No
Is GP lost to follow up? (after 3 contact attempts over a 30-day window)	◯ Yes ◯ No
Number of HCV notifications associated with GP?	◯ One ◯ Two ◯ Three ◯ Four ◯ Five

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Appendix C: Notification questionnaire

This is the Notification form, which will record information about each eligible Notification
GPs can have multiple notification during the study period.

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A randomised controlled trial of active case management to link hepatitis C notifications to hepatitis C treatment in Tasmania

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Notification form

GP ID (REDCap assigned)

_____

This is the Notification form, which will record information about the eligible Notification. GP: [record_id], [gp_name] Arm: [treat] GP consent: [gp_consent] Please only fill in Notifications Forms if GP has consented to participate in our study! This needs to be specified in the GP Form

Enter Notification ID

_____

Enter Resident (Patient) ID

_____

WARNING: Notification ID cannot be the same as Patient ID.

What is the lab notification received date on the notification?

_____

Is this notification a confirmed or repeat notification?

- ◯ Confirmed (Ab+)
- ◯ Confirmed (PCR+)
- ◯ Repeat (Ab+)
- ◯ Repeat (PCR+)

WARNING: Since this notification is a [notification], please check whether patient [patient_id] has already enrolled in the study with another notification.

- ◯ No, patient [patient_id] is new to the study
- ◯ Yes, patient [patient_id] has already enrolled in our study with same GP [gp_name]
- ◯ Yes, patient [patient_id] has already enrolled in our study with DIFFERENT GP

Is there a related Notification ID to this [notification] notification?

- ◯ Yes
- ◯ No

What kind of notification is the related Notification ID?

- ◯ Confirmed PCR+
- ◯ Repeat Ab+
- ◯ Repeat PCR+
- ◯ Confirmed Ab+

Enter related [related_id_2] Notification ID

_____

WARNING: The related notification ID cannot be the same as the current notification ID.

WARNING: The related notification ID cannot be the same as the patient ID.

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What is the date of the related notification?

_____

Is GP same for [related_id_2] Notification ID [related_id_3]?

◯ Yes
◯ No

Is the other GP participating in this study?

◯ Yes
◯ No

Enter GP ID

_____

WARNING: same ID as GP ID.

1. Clinical summary for Notification ID [notification_id]

Please fill in at time of lab notification received date: [lab_date]

	detected	not detected	not tested	testing to follow (test ordered)	Unknown
Hepatitis C Antibody (Anti-HCV)	◯	◯	◯	◯	◯
Hepatitis C Virus by Nucleic Acid Testing (PCR or HCV RNA)	◯	◯	◯	◯	◯

WARNING: This combination is not correct.

What is RNA test date on the notification?

_____
(Note that for a repeat PCR the lab date is the same as the RNA date)

2. Enhanced Form

For Confirmed (Ab+) notifications only

Has enhanced form been sent back by GP?

◯ Yes
◯ No
◯ Unknown
◯ N/A

What is the Enhanced Form date (date reviewed by DoH)?

_____

Has this person had a negative hepatitis C antibody test within the past 24 months?

◯ No
◯ Yes
◯ Unknown

Date of last negative test

_____

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Confirmation that this infection was notified previously Interstate and to the National Notifiable Diseases Surveillance System?	◯ Yes, record as Previously Notified Interstate ◯ No, Confirmation Status remains Confirmed

Has patient had any of the following risk exposures (please tick all options that apply for each risk exposure)

	Yes (within last 2 years)	Yes (over 2 years ago)	No	Unknown
Injecting drug use	◯	◯	◯	◯
Imprisonment	◯	◯	◯	◯
Sexual partner of opposite sex with HCV	◯	◯	◯	◯
Sexual partner of same sex with HCV	◯	◯	◯	◯
Household contact with HCV	◯	◯	◯	◯
Perinatal transmission	◯	◯	◯	◯
Tattoos	◯	◯	◯	◯
Acupuncture	◯	◯	◯	◯
Ear or body piercing	◯	◯	◯	◯
Occupational needlestick/biohazard injury in non- healthcare worker	◯	◯	◯	◯
Non-occupational needlestick/biohazard injury (other than IDU)	◯	◯	◯	◯

3. Patient information of Patient [patient_id]

Age	__________________________________
Gender	◯ Male ◯ Female ◯ Other ◯ Unknown

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In which LGA does the patient live?	◯ Break O'Day ◯ Brighton ◯ Burnie ◯ Central Highlands ◯ Central Coast ◯ Circular Head ◯ Clarence ◯ Derwent Valley ◯ Devonport ◯ Dorset ◯ Flinders ◯ George Town ◯ Glamorgan/Spring Bay ◯ Glenorchy ◯ Hobart ◯ Huon Valley ◯ Kentish ◯ King Island ◯ Kingborough ◯ Latrobe ◯ Launceston ◯ Meander Valley ◯ Northern Midlands ◯ Sorell ◯ Southern Midlands ◯ Tasman ◯ Waratah/Wynyard ◯ West Coast ◯ West Tamar ◯ Unknown
Has patient had previous HCV treatment?	◯ Yes ◯ No ◯ Unknown ◯ N/A
Previous HCV treatment outcomes	◯ Patient had a sustained virological response (SVR) >12 weeks post treatment ◯ Patient did not have a sustained virological response (SVR) >12 weeks post treatment ◯ Unknown

4. Contact with GP for this notification Please specify if any contact with GP. When: Intervention arm: 2 weeks - 3 months Control arm: 3 months (for intervention arm, information can be updated through 3 month period.)

Have you been able to contact the GP for this Notification?	◯ Yes ◯ No (Please use a 30-day period to try to contact GP)
How many call attempts prior to reaching GP for this Notification?	_____ (Please specify the total number. Leave blank if unknown.)
How many call attempts were made to reach GP for this Notification?	_____ (Please specify the total number. Leave blank if unknown.)

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For GPs in the Control arm: has GP returned Enhanced Form (CRF) and/or did you call?	☐ GP had filled in our form and sent back ☐ GP was called ☐ Other (specify) (Check all that apply.)
Other reason why enhanced form not returned	_____
What is the reason this GP cannot be contacted for this notification?	◯ GP is no longer working at the practice ◯ GP referred patient to specialist care ◯ GP declined to be contacted ◯ Practice no longer exists ◯ Unable to access contact details for the GP ◯ Other (specify)
Other (specify)	_____

5. Assistance required

Intervention arm only.

Please specify the assistance required by [gp_name] for this notification.

What kind of assistance does the GP need in managing Hepatitis C care/ what questions do they have?	☐ Level 1: Information on the virus ☐ Level 2: Further testing advice ☐ Level 2: Conducting pre-treatment work-up assessment ☐ Level 3: DAA prescription guidelines, including linkage to specialist consultation ☐ Level 3: Advising on conducting post-cure management including methods of follow-up to manage risks; including harm minimization, reducing re-infection risk, opioid substitution therapy ☐ Level 3: Linking/referral to resources for patients with cirrhosis or other concerns to specialist support for ongoing management ☐ Level 4: Direct patient contact ☐ Other (Check all that apply.)
Please specify "other"	_____

6. Calls and contact with GP or Patient

Intervention arm only.

Please specify the calls that you have had with this GP over the 3 month period. Check all that apply

You can update this information any time during the 3-month intervention period

	Call 1	Call 2	Call 3	Call 4	Call 5

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Choose moments of contact with GP or Patient	☐	☐	☐	☐	☐

Please specify the date of the first contact

_____

Please specify duration of first call in minutes

_____
(Please leave blank if unknown.)

Were prior call attempts made before successful contact?
○ Yes
○ No

Details of unsuccessful prior calls

_____

Was this call with the GP or the patient?
○ GP
○ Patient

Please specify the date of the second call

_____

Please specify duration of second call in minutes

_____
(Please leave blank if unknown.)

Were prior call attempts made before successful contact?
○ Yes
○ No

Details of unsuccessful prior calls

_____

Was this call with the GP or the patient?
○ GP
○ Patient

Please specify the date of call 3

_____

Were prior call attempts made before successful contact?
○ Yes
○ No

Details of unsuccessful prior calls

_____

Please specify duration of call 3 in minutes

_____
(Please leave blank if unknown.)

Was this call with the GP or the patient?
○ GP
○ Patient

Please specify the date of call 4

_____

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Were prior call attempts made before successful contact?	○ Yes ○ No
Details of unsuccessful prior calls	_____
Please specify duration call 4 in minutes	_____ (Please leave blank if unknown.)
Was this call with the GP or the patient?	○ GP ○ Patient
Please specify the date of the call 5	_____
Were prior call attempts made before successful contact?	○ Yes ○ No
Details of unsuccessful prior calls	_____
Please specify duration of call 5 in minutes	_____ (Please leave blank if unknown.)
Was this call with the GP or the patient?	○ GP ○ Patient
Document other modes of communication with GP if applicable e.g. sending GESA guidelines or other links.	_____

7. Level of assistance provided

Intervention arm only.

Please specify the level of assistance provided to GP [gp_name] for this notification at the end of 3-month period.

Has assistance been provided to GP?	○ yes ○ no
Level of assistance provided to GP [gp_name] for this Notification	☐ level 1: information ☐ level 2: testing, awareness, pre-treatment work-up ☐ level 3: DAA guidelines, treatment support, post-cure management, referral to specialist ☐ level 4: direct patient contact ☐ other (Check all that apply.)
Please specify 'other'.	_____

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During which call did you start the intervention?	◯ call 1 ◯ call 2 ◯ call 3 ◯ call 4 ◯ call 5 ◯ unknown
During the direct-patient call, what intervention has been done?	☐ Referral back to GP ☐ Referred to online resources ☐ Direct information to patient (Check all that apply.)
WARNING: This call has not been recorded above.	
Has GP finished the intervention? (i.e. all required assistance has been provided to GP)	◯ Yes ◯ No ◯ Other (specify)
Other intervention outcomes?	_____
Why not?	◯ could not reach GP ◯ GP did not want to be called back again ◯ other ◯ patient is lost to follow up ◯ unknown
During which call did you finish the intervention?	◯ call 1 ◯ call 2 ◯ call 3 ◯ call 4 ◯ call 5 ◯ unknown
WARNING: This call has not been recorded above.	

8. Outcomes

Intervention arm and Control arm.

Please specify the outcomes (testing and treating) after 3 months

Please provide the date of recording information on the outcomes	_____
Has RNA test been ordered yet?	◯ Yes ◯ No ◯ Unknown ◯ Yes, but by another GP ◯ Yes, but by a specialist
What do you think is the number 1 barrier for not RNA testing this Notification?	◯ Patient lost to follow up (no longer engaged in care at this clinic) ◯ Patient needed to be referred to specialist ◯ Patient refused to undergo puncture ◯ Unsuccessful attempts at blood draw ◯ Other (specify)

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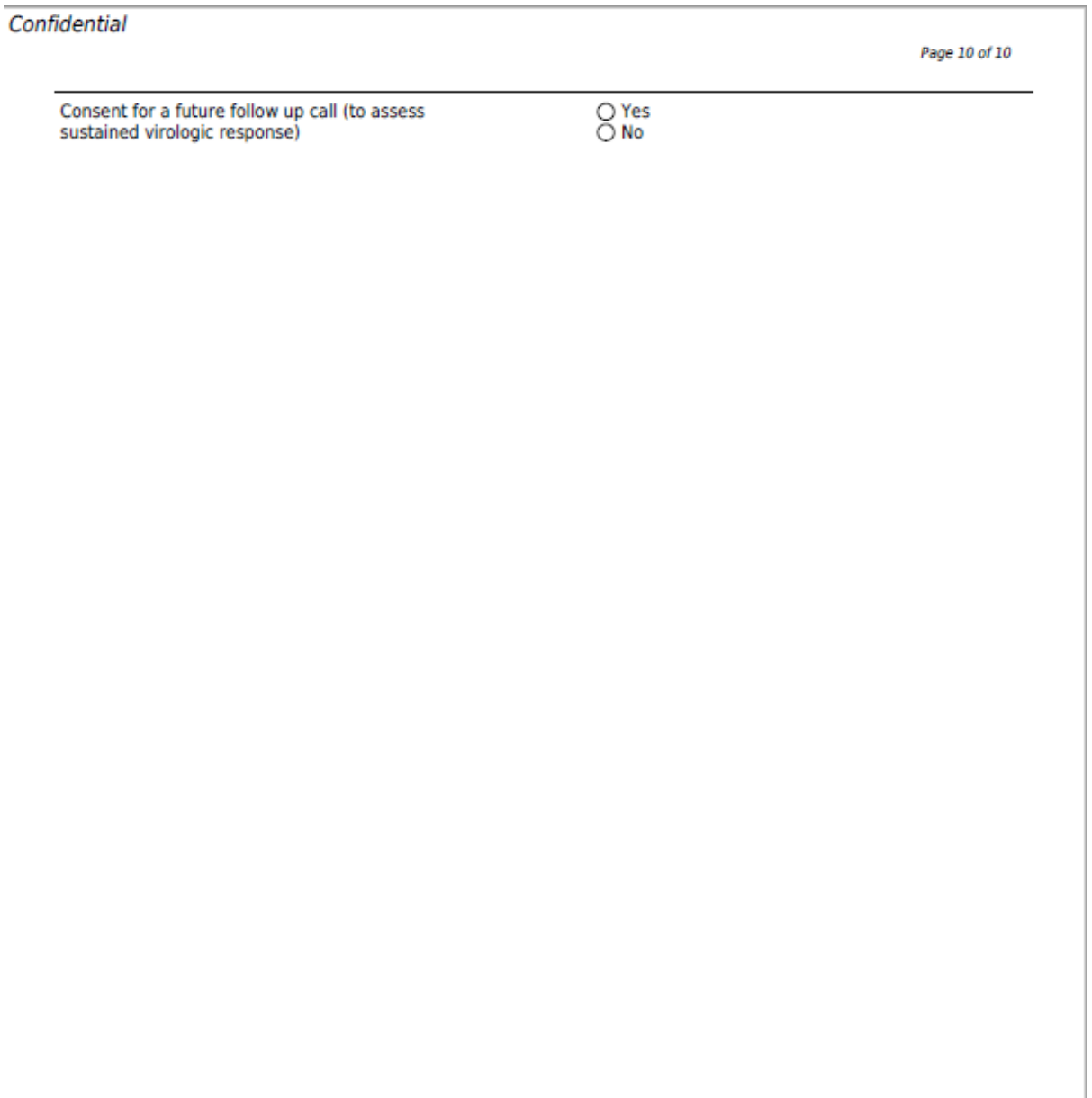
Please specify other barrier for no RNA testing	_____
Have results come back yet?	◯ Yes ◯ No ◯ Unknown
What is RNA test date?	_____ (Note that for a repeat PCR the lab date is the same as the RNA date)
What was the result of the HCV RNA test	◯ Detected ◯ Not detected ◯ Indeterminate
Were appropriate pre-treatment work-up blood tests collected e.g. full blood count (platelet count), liver enzymes (AST)	◯ Yes ◯ No
What is the number 1 barrier for no pre-treatment work-up blood tests	◯ Patient is lost to follow-up ◯ Patient declined blood draw ◯ Patient was referred to a specialist ◯ Patient transferred to another practice ◯ Other (specify)
Other pre-treatment blood work up barriers	_____
Has GP written a DAA script for this notification?	◯ Yes ◯ No ◯ Unknown
What is the number 1 barrier for not writing a DAA script?	◯ Patient is lost to follow-up at the practice ◯ Patient has transferred to another practice ◯ Patient was transferred to a specialist ◯ Patient declined treatment ◯ Other (specifiy)
Other reason for no DAA script	_____
Has treatment already started?	◯ Yes ◯ No ◯ Unknown
What is the treatment start date?	_____
What do you think is the number 1 barrier for not treating this Notification?	◯ Patient lost to follow up ◯ Patient needed to be referred to specialist ◯ Patient refused treatment ◯ Other
Please specify other barrier for not treating	_____



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Consent for a future follow up call (to assess sustained virologic response)	○ Yes ○ No

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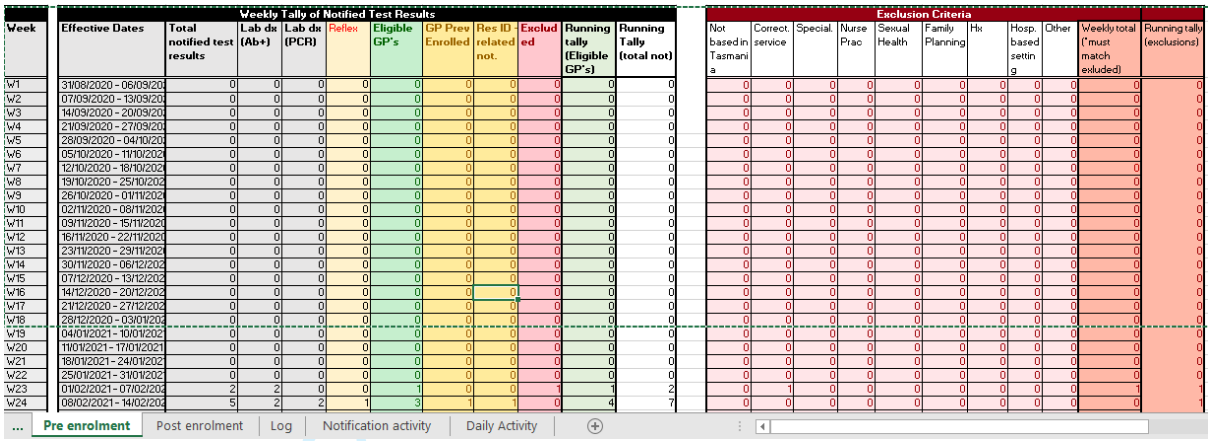
Appendix D: Screening Log



Week	Effective Dates	Weekly Tally of Notified Test Results: Total notified test results	Lab dx (Ab+)	Lab dx (PCR)	Reflex	Eligible GP's	GP Prev Enrolled	Res ID related not.	Excluded	Running tally (Eligible GP's)	Running Tally (total not)	Exclusion Criteria: Not based in Tasmania	Correct. service	Special.	Nurse Prac	Sexual Health	Family Planning	Hx	Hosp. based settin g	Other	Weekly total (*must match exluded)	Running tally (exclusions)
W1	31/08/2020 - 06/09/20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W2	07/09/2020 - 13/09/20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W3	14/09/2020 - 20/09/20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W4	21/09/2020 - 27/09/20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W5	28/09/2020 - 04/10/20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W6	05/10/2020 - 11/10/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W7	12/10/2020 - 18/10/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W8	19/10/2020 - 25/10/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W9	26/10/2020 - 01/11/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W10	02/11/2020 - 08/11/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W11	09/11/2020 - 15/11/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W12	16/11/2020 - 22/11/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W13	23/11/2020 - 29/11/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W14	30/11/2020 - 06/12/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W15	07/12/2020 - 13/12/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W16	14/12/2020 - 20/12/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W17	21/12/2020 - 27/12/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W18	28/12/2020 - 03/01/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W19	04/01/2021 - 10/01/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W20	11/01/2021 - 17/01/2021	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W21	18/01/2021 - 24/01/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W22	25/01/2021 - 31/01/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W23	01/02/2021 - 07/02/20	2	2	0	0	1	0	0	1	1	2	0	1	0	0	0	0	0	0	0	1	1
W24	08/02/2021 - 14/02/20	5	2	2	1	3	0	1	0	4	7	0	0	0	0	0	0	0	0	0	0	1

... | Pre enrolment | Post enrolment | Log | Notification activity | Daily Activity

Appendix E: Sample size calculations

The sample size calculation is powered to cover a range of the most probable and realistic assumptions.

1. Treatment uptake in standard of care arm: Existing data estimates between 3-8% of people start therapy within three months (when our primary outcome will be assessed): data on national treatment uptake by specialists and general practitioners,[16] among people who inject drugs,[17] and in traditional referral to outpatient services all estimate treatment uptake of 8% or under at three months.[18] In this study, we will assume the higher (and therefore more conservative, biasing towards the null hypothesis) estimate of treatment uptake of 8% at three months in the control arm.

2. Treatment uptake in intervention arm: is estimated at 25% based on best estimates of intervention acceptance by GPs and follow up, RNA prevalence among those notified with HCV antibody, community treatment eligibility, and best estimate of intervention effect.

- Acceptance and participation of general practitioners is estimated at 90% at 3 months based on general practice acceptance of prescribing support (fewer than 10% of South Australian general practitioners declined SA Health support during remote follow up; unpublished data).

- RNA prevalence among those HCV-antibody positive has been measured 50-70% in surveillance data over the past 10 years.[19]

- Community treatment eligibility has been observed at 88% (10% cirrhosis, and 2% HIV or HBV coinfection or other serious comorbidities) in our Australian community treatment trials.[20]

- Intervention of primary care support is estimated to see 65% of eligible patients start on treatment at three months. We have informed this estimate based on pilot data from primary care support provided in Victorian models of support for general practitioners (91% treatment uptake among HIV-prescribers[21]; 74% treatment uptake in testing support models in community settings[22]; 71% follow up for treatment in a South Australian model of health department remote follow up, unpublished data). We have conservatively assumed a lower rate of treatment uptake among all eligible, viraemic patients of 65%.

Based on the most conservative of these assumptions, we estimate 25% (i.e., 0.90 x 0.50 x 0.88 x 0.65) of individuals in the intervention arm will commence treatment.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1,4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	4,5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5,6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	10
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	N/A

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	N/A
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	N/A
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	N/A
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	N/A
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	N/A
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	N/A
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	N/A
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	1
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	14

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

A RANDOMISED CONTROLLED TRIAL OF ACTIVE CASE MANAGEMENT TO LINK HEPATITIS C NOTIFICATIONS TO TREATMENT IN TASMANIA, AUSTRALIA – A STUDY PROTOCOL

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Secondary Subject Heading:	Epidemiology
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A RANDOMISED CONTROLLED TRIAL OF ACTIVE CASE MANAGEMENT TO LINK HEPATITIS C NOTIFICATIONS TO TREATMENT IN TASMANIA, AUSTRALIA – A STUDY PROTOCOL

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Word Count: 3,964

Abstract

Introduction

By subsidising access to direct acting antivirals (DAAs) for all people living with hepatitis C (HCV) in 2016, Australia is positioned to eliminate HCV as a public health threat. However, uptake of DAAs has declined over recent years and new initiatives are needed to engage people living with HCV in care. Active follow up of HCV notifications by the health department to the notifying general practitioner (GP) may increase treatment uptake. In this study, we explore the impact of using hepatitis C notifications systems to engage diagnosing GPs and improve patient access to treatment.

Methods and analysis

This study is a randomised controlled trial comparing enhanced case management of HCV notifications with standard of care. The intervention includes phone calls from a department of health (DoH) specialist HCV nurse to notifying GPs and offering HCV management support. The level of support requested by the GP was graded in complexity: level one: HCV information only; level two: follow up testing advice; level three: prescription support including linkage to specialist clinicians; and level four: direct patient contact. The study population includes all GPs in Tasmania who notified HCV diagnosis to the DoH between September 2020 and December 2021.

The primary outcome is proportion of HCV cases who initiate DAAs after 12 weeks of HCV notification to the health department. Secondary outcomes are proportion of HCV notifications that complete HCV RNA testing, treatment work-up, and treatment completion. Multiple logistic regression modelling will explore factors associated with the primary and secondary outcomes. The sample size required to detect a significant difference for the primary outcome is 85 GPs in each arm with a two-sided alpha of 0.05 and 80% power.

Ethics and dissemination

The study was approved by University of Tasmania's Human Research Ethics Committee (Protocol ID: 18418) on 17 December 2019. Results of the project will be presented in scientific meetings and published in peer-reviewed journals.

Registration details

The trial is registered on ClinicalTrials.gov (ID: NCT04510246)

Trial progression

The study commenced recruitment in September 2020 and end of study expected December 2021.

STRENGTHS AND LIMITATIONS

- This is the first randomised study utilising disease notifications data to determine effectiveness of supporting linkage to HCV care and treatment.
- This trial is examining the effectiveness of guiding care pathways for prospectively notified diagnoses.
- There is a risk of contamination of the intervention if GPs at the same clinic are randomised to different arms of the study, which might under-estimate the true benefit.
- The study runs a risk of high loss to follow up particularly with locum GPs as they move across practices.

Introduction

Hepatitis C virus (HCV) affects approximately 71 million people globally causing 400,000 deaths each year [1]. In Australia, approximately 180,000 people were estimated to be living with HCV in 2017 [2]. The availability of direct-acting antiviral medications (DAAs) on the Pharmaceutical Benefits Scheme (PBS) since March 2016, has revolutionised HCV care[3]. The simplicity and tolerability of these new treatments, combined with Australia providing largely unrestricted access to DAAs in primary care, makes it possible for Australia to eliminate HCV as a public health threat [4, 5].

To realise this once-in-a-generation opportunity, it is imperative that sufficient numbers of people complete treatment in order to interrupt transmission [5]. While in the initial year of DAA subsidy in 2016 over 32,000 treatments were prescribed, the number of people commencing treatment has declined considerably; in 2019, 11,580 DAA treatments were prescribed [6], below the estimated 13,680 annual treatments needed to achieve HCV elimination in Australia by 2030 [7]. As such, initiatives are needed to actively engage people living with hepatitis C in care and ensure that health care providers are appropriately equipped to prescribe DAAs or link patients to treatment.

DAAs can be prescribed by general practitioners (GPs) in Australia and they provide an additional accessible and convenient HCV care and treatment pathway. The proportion of Australians receiving DAA treatment via their GP increased from 8% at the introduction of DAAs in March 2016 to 40% in May 2017, but has remained stable since [6]. There are clear guidelines available for hepatitis C treatment, and the introduction of pan-genotypic regimens in August 2017 has further simplified treatment options [3]. However, DAA access barriers remain, particularly for people who inject drugs who are a key group for hepatitis C elimination efforts [5]. Qualitative research amongst both consumers and providers of health care has suggested that a lack of provider follow-up and support is a barrier to treatment uptake after diagnosis [8-10].

Hepatitis C is a notifiable disease in Australia and notifications represent an opportunity to link patients to treatment. Consistent with other Australian jurisdictions, in Tasmania, the setting for this study, laboratories conducting hepatitis C testing notify positive hepatitis C test results to the Department of Health (DoH) using the details of the GP who ordered the test [11] in accordance with Communicable Disease Network of Australia Hepatitis C surveillance case definition [12]. This study is the first randomised controlled trial to assess the impact of active case follow-up of hepatitis C notifications using a jurisdiction-wide disease notifications system to support linkage to care and treatment. A non-randomized pilot study in England explored the use of a half-time facilitator who trained key workers, supported hepatology appointments, and interacted directly with clients[13]. The half-time facilitator led to increased engagement and treatment uptake among people who inject drugs with hepatitis C. Other studies utilised strategies to increase HCV testing and treatment using community drug services and not surveillance data [14, 15] and were not prospective study designs [16, 17].

This study designates a DoH specialist HCV nurse embedded within the Tasmanian DoH to contact GPs and provide supported assistance after a hepatitis C diagnosis is notified. The study will evaluate whether active follow up of providers with enhanced case management is more effective in enhancing uptake of hepatitis C treatment compared to current standard of care for new notifications by the DoH. The study will also compare the cost-effectiveness of the enhanced case management compared to current standard of care for positive hepatitis C antibody notifications.

Methods and analysis

This study is a two-arm, cluster randomised controlled trial with randomisation at the level of the GP who notifies the DoH (directly or through a laboratory) of a hepatitis C antibody positive case.

Study Setting

The study will be conducted in the Australian state of Tasmania with a population of approximately 530,000 [18] and an estimated 3,349 people living with hepatitis C [2]. The preceding ten years have seen an average 260 new hepatitis C notifications in Tasmania annually, with a new notification rate of 48.6 per 100,000 population, slightly higher than the national average of 43.3 per 100,000 population [2]. The entire state will be included in the trial, as all notifications are received and managed by a central body at the Tasmanian DoH.

Standard of care

When a laboratory in Tasmania has a positive hepatitis C antibody test result, they formally notify this case to the DoH. A 'hepatitis C notification' requires laboratory definitive evidence of a positive hepatitis C antibody test or hepatitis C RNA test in a person with no prior evidence of hepatitis C virus infection [12]. Notifications can be further classified by DoH as 'newly-acquired', which is defined by laboratory or clinical evidence that infection occurred within the preceding 24 months [19], and notifications where a person has prior evidence of hepatitis C infection are classified as a 'repeat' notification. Under the Communicable Diseases Network Australia (CDNA) case definitions, 'unspecified' hepatitis C is a confirmed case that is not notifiable, similar to 'repeat' notifications [20]. At present, repeat notifications receive no further follow up by the DoH. In this protocol, the term 'new' notification is used to indicate all notifications that meet the case definition (regardless of whether they are 'newly-acquired' or not), and use the term 'repeat' notifications if the patient has prior evidence of hepatitis C virus infection.

After receipt of a hepatitis C notification, surveillance officers check the details of the case to determine whether the test represents a new or repeat notification. For cases determined to represent a 'new' notification, a request for further details of the case is mailed to the medical practitioner who requested the test. A routine surveillance letter and an enhanced surveillance data collection form are mailed to the GP. The aim of this request is to accurately capture surveillance data that pertains to testing history and risk factors. Advice on how to manage hepatitis C is also included in the routine surveillance letter. On assessment of returned enhanced surveillance data collection form, the DoH may undertake further risk assessment, investigation and response activities. If the practitioner does not return the enhanced surveillance data collection form within 20 days, the form is re-posted to the practitioner. If cases are determined to be a repeat notification the current standard of care is to conduct no further activities regarding this case. Other jurisdictions around Australia follow a similar algorithm and process for managing new notifications.

Participant Eligibility

All GPs who have requested a hepatitis C antibody test that leads to new or repeat notification to the Tasmanian DoH will be eligible for participation in this study. Notifications by GPs not based in Tasmania, from correctional services, sexual health or family planning services as well as specialists, trainees, and nurse practitioners will be excluded.

Randomisation and Allocation

The unit of randomisation is at the GP level and will be done within 3 weeks of HCV notification receipt by the DoH and by the order they are received. GPs will be allocated one-to-one at their first notified case during the follow-up period and all subsequent notifications will receive either standard or care or intervention arm case management consistent with the initial randomisation. This will ensure that standard of care and intervention arms are not cross-contaminated by GPs that make multiple notifications. The sequence will be performed using the randomisation function within REDCap. A representation of randomisation and the study process and activities in each arm is shown in Figure 1. Randomisation will not done for GPs already enrolled and no further action will be required for the enrolled patients (HCV notifications).

Blinding

Given the nature of the intervention, it is impossible to blind either the DoH specialist HCV nurse or the GP to allocation. Analyses will be independently conducted by analyst statistician at the Burnet Institute who will be blinded to intervention allocation.

Description of Intervention

Intervention Arm

GPs randomised to the intervention arm will receive the standard of care surveillance letter, enhanced surveillance data collection form for new hepatitis C notifications, and a study information letter (Supplementary material, Appendix A). In addition to standard of care procedures, all notifications (new and repeat) will be offered further enhanced case management support by a DoH specialist HCV nurse. Support is offered at the initial phone call, and is made available over a 12-week period during which the DoH specialist HCV nurse can do follow-up calls with the GP or directly with the patient.

Initial phone call

Within 3 weeks of the HCV notification being received by the DoH, GPs randomised to the intervention arm will receive an initial phone call from the DoH specialist HCV nurse. During this call, GPs are consented into the study and offered enhanced case management support in line with approved guidelines for hepatitis C management [3]. Three attempts will be made to contact the practitioner within a 30-day period before they are classified as lost to follow-up.

The DoH specialist HCV nurse will initially confirm the notification made by the with GP and ask if the: 1) patient had been recalled for further management; 2) whether a hepatitis C RNA test has been ordered; and 3) of any RNA positive patient, whether treatment options had been discussed, offered or initiated. A tailored level of enhanced case management support is then offered depending on RNA status (if no RNA testing, offer level 1 & 2), GPs needs (offer level based on GP preferences after assessing RNA status), and familiarity with HCV prescribing (Model 1), and support needed for their patient (Model 2). Level 4 is optional for the GP and will be offered upon request or when the DoH specialist HCV nurse identifies a need based on assessment.

Enhanced case management support for GP (Model 1)

Level 0: No assistance required, GP already confident in managing HCV treatment
Level 1: General information on hepatitis C care and treatment
Level 2: Further diagnostic testing advice and support to conduct pre-treatment work-up assessment

Level 3: DAA prescription guidelines including that treatment can be prescribed by the GP and when/how to refer for specialist care.

- Advising on conducting post-cure management including methods of follow-up to manage risks; including harm minimization, reducing re-infection risk, opioid substitution therapy
- Linking/referral to resources for patients with cirrhosis or other concerns to specialist support for ongoing management

The GP may indicate the preference to receive the enhanced case management support via several phone calls or emails.

Enhanced case management for patient (Model 2)

Level 4: Direct patient contact

The GP will also be offered the option of the DoH specialist HCV nurse contacting the patient directly with their consent to notify them of their result and inform them about further testing and treatment options and referral back to their GP or other primary care or specialist. Model 2 is an option for GPs at any level of support in Model 1.

Evaluation follow up (intervention)

As with the standard of care arm, GPs in the intervention arm will be contacted by telephone call 12 weeks after an HCV notification date to complete the details of the patient outcomes for the specific case. Details provided or missing from the standard DoH enhanced surveillance data collection form will be confirmed with the GP at this phone call (see figure 1). Similar to the standard of care arm, three call attempts will be made to contact the practitioner within a 30-day period prior to classifying the GP as lost to follow-up.

Evaluation follow up (standard of care)

All GPs randomised to the standard of care arm will be contacted by telephone 12 weeks after the HCV notification date (see figure 1). Two weeks prior to the evaluation phone call, a study information letter (Supplementary material, Appendix A) will be sent to the GP. This is not current standard practise but will be performed by the DoH specialist HCV nurse for the project outcome evaluation. During this phone call consent will be sought for the GP to provide information about their clinical management of the notified patient. Details provided or missing from the standard enhanced surveillance data collection form would be confirmed with the GP at this phone call. Three attempts to contact the practitioner will be made within a 30-days of receipt of the hepatitis C notification before they are classified as lost to follow-up.

Outcomes

Primary outcome

The primary outcome is the proportion of cases notified with hepatitis C who commence hepatitis C treatment within 12 weeks of HCV notification as evidenced by confirmation from the GP. This will be assessed using the information provided by GPs at the evaluation phone call and will be compared across the two arms and the model and level of support offered.

Secondary outcomes

At the evaluation phone call for both the standard of care and intervention arm, additional outcome measures will be collected which we will collate into:

- Proportion of people diagnosed with hepatitis C antibody with a documented HCV RNA test result;
- Proportion of people diagnosed with hepatitis C (HCV RNA+) completing treatment work-up blood tests;
- Proportion of people diagnosed with hepatitis C (HCV RNA+) completing an appropriate course of hepatitis C treatment as prescribed.

To evaluate patient-factors that may have an impact on the likelihood of people commencing hepatitis C treatment, the project will utilise de-identified aggregated data from the DoH obtained through the standard surveillance procedures in determining risk exposures, age, gender and date of diagnosis. The likelihood of commencing support will also be evaluated by model and level of support and number and types of contacts made.

Data Collection

The first data point collection will be completed by the DoH specialist HCV nurse when conducting the initial telephone call to the GPs in the intervention arm to confirm eligibility and consent (Supplementary material, Appendix B). No identifying patient details will be recorded for the evaluation of the project: any clinical information that the DoH specialist HCV nurse and the GP discuss for clinical management of individuals is not collected for the purpose of this project. Data collected from participating GPs will be allocated a study identification (ID) and a patient ID for the case with HCV (Supplementary material, Appendix C).

The second format of data collection will concurrently record the nature of the activities (level of support, HCV notification details) and time taken to complete them by the DoH specialist HCV nurse as part of the hepatitis C management assistance provided to the practitioner. This will be recorded in an excel spreadsheet, using the numerical participant's/GP 's study ID (Supplementary material, Appendix D). This information will enable determination of the costs of the intervention, to inform cost-effectiveness estimates. No identifying patient details will be sought or recorded for the purpose of the evaluation of the project.

The DoH specialist HCV nurse will collate de-identified information for the purpose of the evaluation of the project from the participant/GP of the outcome of HCV care of the notifications. Also, from the DoH standard enhanced surveillance data collection form, any missing data will be collected for standard of care purposes; e.g. dates of testing, the patient's age, gender and risk exposures. For the purpose of the project, de-identified data will be collated from this form for the purpose of the project evaluation. These data will be extracted and stored with a unique patient study number.

Linkage between the patient ID and the GP's study ID will permit evaluation at service provider level which will maintain confidentiality of the participants/GP and patient data.

Data Management

The data from the phone surveys will be collected using REDCap software, and stored in a secure, password protected server at the Burnet Institute. It will be accessible to the DoH specialist HCV nurse, the study coordinator, data analysts at the Burnet Institute and the Institute's data manager. This data will be stored with a unique numerical GP study ID and patient ID.

All data entry will be performed by the DoH specialist HCV nurse based at Tasmanian DoH. A Burnet Institute researcher will check the data quality every month and liaise with the DoH specialist HCV nurse if there are any errors or inconsistencies.

The participant/GP log (Supplementary material, Appendix D) and record of activities and time spent will be kept on a password protected server accessible only to the DoH specialist HCV nurse and study investigators at the Tasmanian Department of Health.

Data will be monitored by a Burnet Institute staff member reviewing the collected data monthly to identify any errors or inconsistencies. Any issues or uncertainties will be followed up with the DoH specialist HCV nurse to clarify meaning of data and ensure robust entry processes.

Statistical Analysis

Sample size

Data supplied by the Tasmanian DoH indicate that in the period from January 2018 to November 2018, taking both repeat and new notifications combined, 274 GPs notified at least one case of hepatitis C; 174 had notified one case, 65 had notified two cases, 14 had notified three cases, and 21 had notified four or more cases. On this basis, an estimated 224 GPs were expected to notify at least one case of hepatitis C during the 9-month study recruitment period.

The sample size required for a parallel design comparing HCV treatment uptake in the standard of care arm of **8%** and **25%** in the intervention arm is 85 GPs in each study arm with a two-sided alpha of 0.05 and 80% power (see Supplementary material, Appendix E). To account for measured correlation between different notifications clustered within the same GP, we used an intra-class correlation coefficient (ICC) of 0.10. Existing data estimates between 3-8% of people start therapy within three months (when our primary outcome will be assessed): data on national treatment uptake by specialists and general practitioners,[21] among people who inject drugs,[22] and in traditional referral to outpatient services all estimate treatment uptake of 8% or under at three months.[23] In this study, we will assume the higher (and therefore more conservative, biasing towards the null hypothesis) estimate of treatment uptake of 8% at three months in the standard of care arm. Treatment uptake in intervention arm is estimated at 25% based on best estimates of intervention acceptance by GPs and follow up, RNA prevalence among those notified with HCV antibody, community treatment eligibility, and best estimate of intervention effect [24-26]. Based on the estimates of 224 unique GPs notifying hepatitis C cases in a 9-month period, there is ample power to detect significant difference between arms even with the presence of clustering of notifications within clinicians.

Analysis of primary outcome

The primary analysis will be assessed as a binary outcome comparing the proportion of patients who commenced treatment in an intention to treat analysis in the Intervention arm compared to the Standard of Care arm.

Analysis of secondary outcomes

Other secondary outcomes will be analysed using the same intention to treat method. A per protocol analysis is proposed.

Multiple logistic regression modelling will explore factors predicting success of aspects of the cascade of care based on information obtained through the notification system, as well as information on the practitioner, associated with the primary and secondary outcomes. Factors to be explored in the multiple regression model include patient sociodemographic, GP's HCV care experience, number of notifications per practitioner, and time taken to reach GP/patient post HCV notification.

There will be no interim analysis or stopping guidelines.

Subsequent research following study completion

Data collection will permit future economic evaluation and cost-effectiveness modelling. Subject to further ethics review, consent may also be sought to contact participants/GPs later to assess rates of treatment success [sustained virological response (SVR)] amongst notified cases who received treatment.

Cost-effectiveness analysis

The cost of this intervention will be compared to the current standard of following up HCV notifications. As cost-effectiveness will depend on the benefits of initiating treatment, and SVR, [27, 28] our estimates will adapt an existing dynamic, deterministic model of HCV transmission, progression and HCV treatment among people living with hepatitis C in order to evaluate the impact of the intervention [29]. The model will stratify HCV notifications by HCV RNA status and intervention pathway and will incorporate HCV infection and disease progression. HCV disease stages will be further divided by HCV RNA status, treatment initiation, and SVR depending on the intervention pathway. A Bayesian parameter sampling and model calibration process will be used to take account of uncertainty in key factors (e.g. HCV disease progression rates, health utilities, death rates, and HCV prevalence) to generate the HCV epidemic profile. Transition rates between disease stages will be taken from previous Australian or UK economic evaluations [30]. Data on treatment uptake, SVR, and costs will be collected by the study. Results will be presented as mean incremental cost-effectiveness ratio (ICER). Probabilistic uncertainty analyses will be used to estimate the uncertainty around the ICER, accounting for uncertainty in the intervention outcomes as well as other cost, behavioural and epidemiological inputs.

Ethics and dissemination

The study was approved by the University of Tasmania's Human Research Ethics Committee (Protocol ID: 18418) on 17 December 2019. GPs in either the Standard of Care arm or in the Intervention arm will be contacted by the DoH specialist HCV nurse will contact the GP by phone, provide an explanation of the study and if the practitioner is interested in participating, verbal consent will be obtained. The project will also use surveillance data collected by the DoH for hepatitis C notifications. The researchers are requested a waiver of consent for the use of the data as it is an existing methods of public health program surveillance.

The results of the project will be presented in scientific meetings and published in peer-reviewed journals. Publication of data derived from the study will be supervised by the Protocol Steering Committee. All published quantitative data will be non-identifiable grouped data, none of which will be specific to a participant/GP. A plain English summary of study outcomes, as well as abstracts from publications, will be available on the Burnet Institute website. Authorship for publications arising from this study will adhere to the International Committee of Medical Journal Editors guidelines [31].

Patient and public involvement

There was no direct patient and public involvement in this protocol development. However, a qualitative exploration of the acceptability of hepatitis C notification systems study conducted with

key informants including those with hepatitis C lived experience informed the study intervention [32].

Discussion

Reaching the World Health Organisation HCV elimination targets will require additional strategies to increase linkage to care and treatment uptake. This is the first prospectively randomised study exploring the utilisation of HCV surveillance data to enhance linkage to HCV treatment. In Australia, HCV is a notifiable infection and the health departments receive notification information which is captured by the surveillance systems. This provides an opportunity to use existing patient information to enhance linkage to care and treatment.

HCV treatment accessed through primary healthcare which includes GPs is fundamental in the Australian healthcare system. Identifying strategies to increase linkage to care and HCV treatment uptake utilising primary health care systems may have a high impact. This study trials an intervention which is post HCV-testing, nurse-led from the department of health. Demonstrating that this nurse-led intervention using existing surveillance systems is feasible can inform further public health strategy planning. The health departments who are custodians of the surveillance data can utilise a nurse or a public health officer to follow through diagnosing clinicians or patients to encourage RNA testing and treatment initiation. If the intervention is shown to be effective, health departments will need to further develop the strategy using appropriate staff and a decision on following up prospective and/or historic HCV notifications.

Trial progress

The study commenced enrolments in September 2020 and the study end is expected in December 2021. Full data analysis will be conducted after the protocol has been published.

References

1. Global hepatitis report 2017. Geneva: World Health Organization; 2017.
2. Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia: annual surveillance report 2018. Sydney: Kirby Institute; 2018.
3. Hepatitis C Virus Infection Consensus Statement Working Group. Australian recommendations for the management of hepatitis C virus infection: a consensus statement (September 2018). Melbourne: Gastroengerological Society of Australia; 2018.
4. Pedrana AE, Sacks-Davis R, Doyle JS, Hellard ME. Pathways to the elimination of hepatitis C: prioritising access for all. Expert Rev Clin Pharmacol. 2017;10(10):1023-6.
5. Scott N, Doyle JS, Wilson DP, Wade A, Howell J, Pedrana A, et al. Reaching hepatitis C virus elimination targets requires health system interventions to enhance the care cascade. Int J Drug Policy. 2017;47:107-16.
6. The Kirby Institute. Monitoring hepatitis C treatment uptake in Australia (Issue 9, July 2018). Sydney: Kirby Institute; 2018.
7. Scott N, Sacks-Davis R, Wade AJ, Stoove M, Pedrana A, Doyle JS, et al. Australia needs to increase testing to achieve hepatitis C elimination. Medical Journal of Australia. 2020;212(8):365-70.
8. Madden A, Hopwood M, Neale J, Treloar C. Beyond interferon side effects: What residual barriers exist to DAA hepatitis C treatment for people who inject drugs? PLoS One. 2018;13(11):e0207226.
9. Skeer MR, Ladin K, Wilkins LE, Landy DM, Stopka TJ. 'Hep C's like the common cold': understanding barriers along the HCV care continuum among young people who inject drugs. Drug Alcohol Depend. 2018;190:246-54.
10. Richmond JA, Wallace J. Implementation of hepatitis C cure in Australia: one year on. J Virus Erad. 2018;4(2):115-7.
11. The Director of Public Health. Guidelines for Notifying Diseases and Food Contaminants. In: Public Health Services TG, Department of Health and Human Services, editor. Tasmania: Tasmanian Government; 2016.
12. Communicable Disease Network Australia. Hepatitis C (unspecified) case definition Canberra: Australian Government Department of Health; 2004 [updated 12th March 200420th February 2019]. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_hepcun.htm.
13. Harrison GI, Murray K, Gore R, Lee P, Sreedharan A, Richardson P, et al. The Hepatitis C Awareness Through to Treatment (HepCATT) study: improving the cascade of care for hepatitis C virus-infected people who inject drugs in England. Addiction. 2019;114(6):1113-22.
14. Palmateer NE, McAuley A, Dillon JF, McDonald S, Yeung A, Smith S, et al. Reduction in the population prevalence of hepatitis C virus viraemia among people who inject drugs associated with scale-up of direct-acting anti-viral therapy in community drug services: real-world data. Addiction. 2021;116(10):2893-907.
15. Harney B, Whitton B, Wade A, Brereton R, Nolan S, Thompson A, et al. A nurse led hepatitis C model of care in primary care and community services in Melbourne, Australia. Journal of hepatology. 2020;73:S795.
16. O'Brien E, Whelan M, Lama T, Levy M. Public Health Unit notifications of hepatitis C and their follow-up in South Western Sydney, Australia. Public Health Research & Practice. 2020.
17. Isfordink CJ, Brakenhoff SM, van Dijk M, van der Valk M, de Knegt RJ, Arends JE, et al. Hepatitis C elimination in the Netherlands (CELINE): study protocol for nationwide retrieval of lost to follow-up patients with chronic hepatitis C. BMJ Open Gastroenterol. 2020;7(1):e000396.
18. Tasmanian Government Economic Analysis Unit. Population (ABS Cat No 3101.0). Hobart: Department of Treasury and Finance, Tasmanian Government; 2018.
19. Communicable Disease Network Australia. Hepatitis C (newly acquired) case definition Canberra: Australian Government Department of health; 2015 [updated 25th September 201520th

February 2019]. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_hepcnew.htm.
20. Communicable Diseases Network Australia. Australian national notifiable diseases and case definitions: CDNA; 2004 [Available from: https://www1.health.gov.au/internet/main/publishing.nsf/Content/cdna-casedefinitions.htm.
21. Doyle JS, Scott N, Sacks-Davis R, Pedrana AE, Thompson AJ, Hellard ME. Treatment access is only the first step to hepatitis C elimination: experience of universal anti-viral treatment access in Australia. Alimentary pharmacology & therapeutics. 2019;49(9):1223-9.
22. Iversen J, Grebely J, Catlett B, Cunningham P, Dore GJ, Maher L. Estimating the cascade of hepatitis C testing, care and treatment among people who inject drugs in Australia. International Journal of Drug Policy. 2017;47:77-85.
23. Wade A, MacDonald DM, Doyle JS, Gordon A, Roberts S, Thompson AJ, et al. The cascade of care for an Australian community-based hepatitis C treatment service. PloS one. 2015;10(e0142770).
24. Burnet Institute and Kirby Institute. Australia's progress towards hepatitis C elimination - Annual Report 2020. Melbourne: Burnet Institute; 2020.
25. Von Bibra S, Doyle JS, Higgs P, Dietze PM, Desmond P, Stoove M, et al. Feasibilty of recruiting people who inject drugs into a nurse-led model of care trial: The TAP study. J Hepatol. 2016;62(2):S817-S8.
26. Doyle JS, Santen DKv, Iser D, Sasadeusz J, O'Reilly M, Harney B, et al. Hepatitis C elimination by enhancing care and treatment among HIV co-infected individuals (the co-EC study): Real world evidence of decreasing HCV incidence and prevalence. J Hepatol. 2019;70:e329.
27. Scott N, Iser DM, Thompson AJ, Doyle JS, Hellard ME. Cost-effectiveness of treating chronic hepatitis C virus with direct-acting antivirals in people who inject drugs in Australia. J Gastroenterol Hepatol. 2016;31(4):872-82.
28. Martin NK, Vickerman P, Miners A, Foster GR, Hutchinson SJ, Goldberg DJ, et al. Cost-effectiveness of hepatitis C virus antiviral treatment for injection drug user populations. Hepatology. 2012;55(1):49-57.
29. Scott N, McBryde E, Thompson AJ, Doyle JS, Hellard ME. Treatment scale-up to achieve global HCV incidence and mortality elimination targets: a cost-effectiveness model. Gut. 2017;66(8):1507-15.
30. Smith DJ, Combellick J, Jordan AE, Hagan H. Hepatitis C virus (HCV) disease progression in people who inject drugs (PWID): A systematic review and meta-analysis. Int J Drug Policy. 2015;26(10):911-21.
31. International Committee of Medical Journal Editors. Defining the role of authors and contributors: International Committee of Medical Journal Editors; 2019 [cited 2019 14th February 2019]. Available from: http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html.
32. Walker S, Wallace J, Latham N, Saich F, Pedrana A, Hellard M, et al. "It's time!": A qualitative exploration of the acceptability of hepatitis C notification systems to help eliminate hepatitis C. International Journal of Drug Policy. 2021;97.

Authors' contributions

JSD, MS, MHH, AP, VW, LO, and AT were involved in the development of the initial idea, methodological design, and drafting the trial protocol for ethics. TM, JSD, and MS prepared the initial protocol manuscript and KPM, JR, KT, SM, FHJ, NS, DI, MV, and TS reviewed and edited the manuscript. TS is the trial statistician. KPM is responsible for data collection and TM is the study coordinator. All authors reviewed and approved the manuscript.

Funding statement

This study is funded by AbbVie as an investigator initiated trial. The study funder will have no role in the study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

Competing interests statement

JD, MS and MH report investigator-initiated research funding to their institution from Gilead Science, AbbVie and Merck. JD reports honoraria for speaking to his institution from Gilead Sciences and AbbVie and MS reports consultant fees from Gilead Sciences. AP has received investigator-initiated grant funding from Gilead Sciences, MSD and Abbvie and speaker fees from Gilead Sciences for unrelated work.

Figure legend

Figure 1: Flowchart of study activities
Green coloured boxes indicated the critical time points in the study. Blue boxes indicate the intervention activities and the evaluation phone call which is made in both study arms.

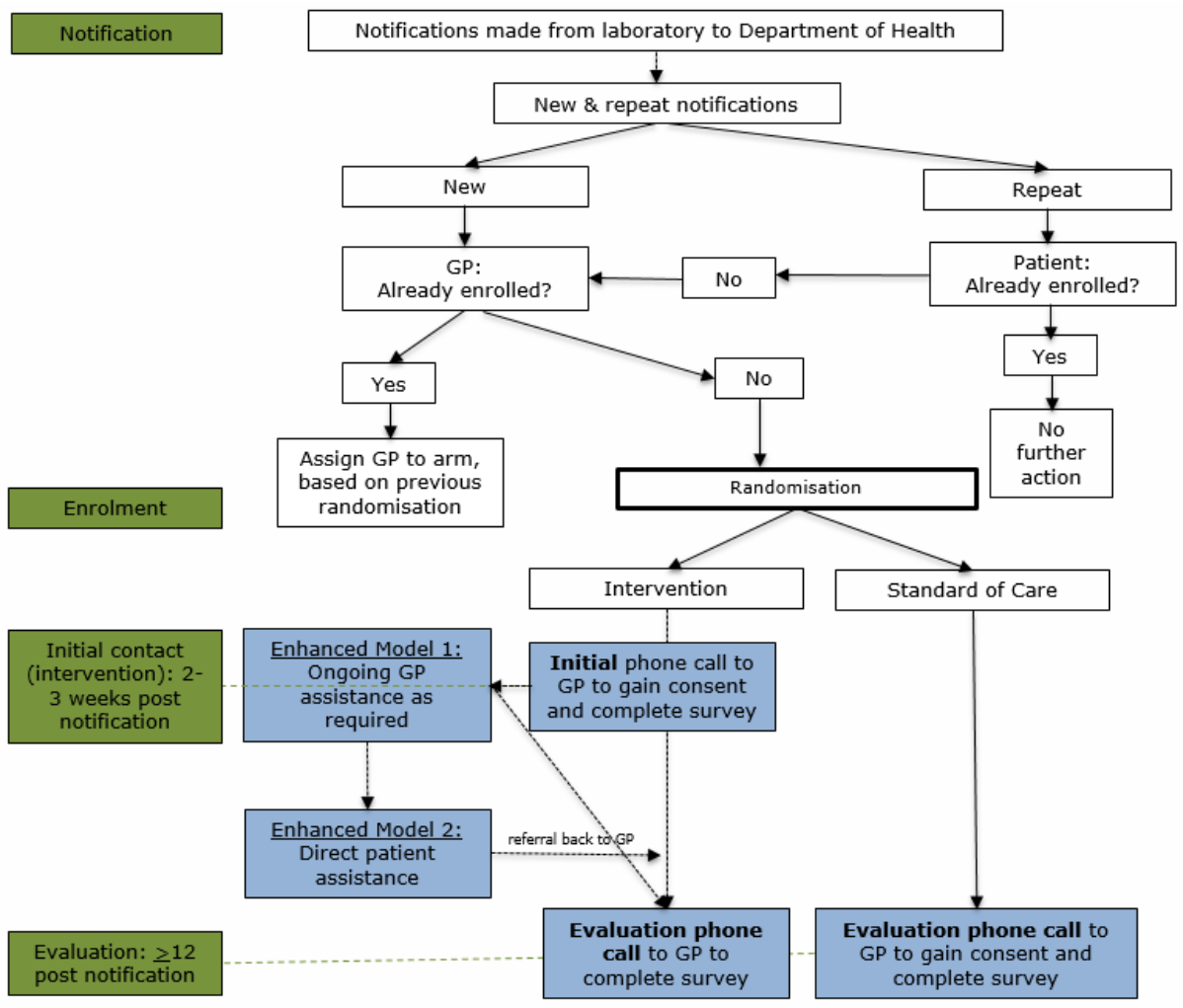

Figure 1: Flowchart of study activities

Green coloured boxes indicate the critical time points in the study. Blue boxes indicate the intervention activities and the evaluation phone call which is made in both study arms.

Supplementary information

Appendix A: Study Information Letter

Rachel Barter | Clinical Nurse Consultant Hepatitis C Research
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«Title» «GP_First_Name» «GP_Last_Name»
«GP_Location»
«GP_Business_Address»
«City» «State» «Post_Code»

«Date»

Dear «Title» «GP_Last_Name»,

Re: Pilot project of active hepatitis C case management for new notifications in Tasmania

The simplicity of new treatments for hepatitis C make it possible for Australia to become one of the first countries to eliminate hepatitis C. **Despite the new treatments becoming available on the Pharmaceutical Benefits Scheme in 2016, half of Australians living with hepatitis C remain untreated[1].**

In accordance with Guidelines under the *Public Health Act 1997*, hepatitis C is a notifiable condition to the Director of Public Health. Public Health Services (Department of Health (DoH), Tasmania) and the Burnet Institute (Melbourne) are conducting a pilot project to determine if a new model of engaging General Practitioners (GPs) who provide care for diagnosed patients will increase treatment uptake (University of Tasmania HREC H0018418).

The project compares current DoH processes following a notification of hepatitis C (standard of care) with active engagement of GPs to provide enhanced case management (new model of care). All GPs in Tasmania who have diagnosed hepatitis C during the study period will be eligible to participate in the project and will be randomly assigned to either the new or standard model of care. This new model will be delivered by a DoH Clinical Nurse Consultant (CNC) who will contact the diagnosing doctor by phone and provide support, as needed, to facilitate hepatitis C pre-treatment testing, treatment, and post-curative support. The Clinical Nurse Consultant will also offer direct patient contact if requested by the GP. A follow-up evaluation phone call will be made to all participating GPs twelve weeks after the initial hepatitis C notification to assess whether enhanced case management results in increased uptake of hepatitis c treatment.

DoH records indicate that you recently requested testing that has resulted in a hepatitis C notification and you have been randomised to participate in the **new model/standard model of care.**

Our CNC Rachel Barter will contact you soon to invite you to participate in this project which we hope you will consider. Verbal consent will be sought on initial phone contact by Rachel. Your involvement will contribute to

[1] Burnet Institute and Kirby Institute. Australia's progress towards hepatitis C elimination: annual report 2019. Melbourne: Burnet Institute; 2019.

a rigorous evidence base for future practice, improve the opportunity for Tasmanians living with hepatitis C to be cured and assist us achieve our hepatitis C elimination goal.

If you wish to talk to Rachel Barter beforehand, please contact her on 6166 0634 or rachel.barter@health.tas.gov.au.

Yours sincerely,

Dr. Mark Veitch
Director, Public Health
Tasmanian Director of Public Health

Dr. Joseph Doyle MPH PhD FRACP FAFPHM
Infectious Diseases Physician
Deputy Director, Disease Elimination Program
Burnet Institute

Appendix B: GP questionnaire

This is the GP Form which will collect data on the GP and will randomise the GP using the REDCap tool online. This needs to be filled in only once for every GP.

A randomised controlled trial of active case management to link hepatitis C notifications to hepatitis C treatment in Tasmania

Page 1 of 2

GP Form

GP ID (REDCap assigned)	_____
GP ID_TNDD (as assigned by TNDD)	_____
Name of GP	_____
What is the postcode of the clinic where this GP works?	_____
Alternative postcode	_____

Please provide some information for GP ID [record_id]

Please confirm that all eligibility criteria for GP have been met	◯ Yes ◯ No
Group to which GP has been randomised	◯ Standard of Care ◯ Intervention
Has GP been reached yet?	◯ Yes ◯ No
Please confirm that GP consents to participate in the study	◯ Yes ◯ No
Please close this form and do not use this GP ID anymore.	
Please provide reason why GP is not willing to consent	◯ Time constraints ◯ Privacy issues ◯ Know enough about HCV ◯ Patient already referred to a specialist ◯ Patient no longer attends practice, transferred ◯ Patient is lost to follow up ◯ Declined to give a reason ◯ Other
Please specify 'other'	_____
Does GP have previous experience in HCV care?	◯ Yes ◯ No
Have you ever written a DAA script?	◯ Yes ◯ No

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Please close this form and do not use this GP ID anymore.	
Has the GP been reached at the 12 week evaluation phone call?	◯ Yes ◯ No
Is GP lost to follow up? (after 3 contact attempts over a 30-day window)	◯ Yes ◯ No
Number of HCV notifications associated with GP?	◯ One ◯ Two ◯ Three ◯ Four ◯ Five

Appendix C: Notification questionnaire

This is the Notification form, which will record information about each eligible Notification
GPs can have multiple notification during the study period.

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A randomised controlled trial of active case management to link hepatitis C notifications to hepatitis C treatment in Tasmania
Page 1 of 10

Notification form

GP ID (REDCap assigned)

_____

This is the Notification form, which will record information about the eligible Notification. GP: [record_id], [gp_name] Arm: [treat] GP consent: [gp_consent] Please only fill in Notifications Forms if GP has consented to participate in our study! This needs to be specified in the GP Form

Enter Notification ID

_____

Enter Resident (Patient) ID

_____

WARNING: Notification ID cannot be the same as Patient ID.

What is the lab notification received date on the notification?

_____

Is this notification a confirmed or repeat notification?

- ◯ Confirmed (Ab+)
- ◯ Confirmed (PCR+)
- ◯ Repeat (Ab+)
- ◯ Repeat (PCR+)

WARNING: Since this notification is a [notification], please check whether patient [patient_id] has already enrolled in the study with another notification.

- ◯ No, patient [patient_id] is new to the study
- ◯ Yes, patient [patient_id] has already enrolled in our study with same GP [gp_name]
- ◯ Yes, patient [patient_id] has already enrolled in our study with DIFFERENT GP

Is there a related Notification ID to this [notification] notification?

- ◯ Yes
- ◯ No

What kind of notification is the related Notification ID?

- ◯ Confirmed PCR+
- ◯ Repeat Ab+
- ◯ Repeat PCR+
- ◯ Confirmed Ab+

Enter related [related_id_2] Notification ID

_____

WARNING: The related notification ID cannot be the same as the current notification ID.

WARNING: The related notification ID cannot be the same as the patient ID.

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What is the date of the related notification?

_____

Is GP same for [related_id_2] Notification ID [related_id_3]?

- ◯ Yes
- ◯ No

Is the other GP participating in this study?

- ◯ Yes
- ◯ No

Enter GP ID

_____

WARNING: same ID as GP ID.

1. Clinical summary for Notification ID [notification_id]

Please fill in at time of lab notification received date: [lab_date]

	detected	not detected	not tested	testing to follow (test ordered)	Unknown
Hepatitis C Antibody (Anti-HCV)	◯	◯	◯	◯	◯
Hepatitis C Virus by Nucleic Acid Testing (PCR or HCV RNA)	◯	◯	◯	◯	◯

WARNING: This combination is not correct.

What is RNA test date on the notification?

_____

(Note that for a repeat PCR the lab date is the same as the RNA date)

2. Enhanced Form

For Confirmed (Ab+) notifications only

Has enhanced form been sent back by GP?

- ◯ Yes
- ◯ No
- ◯ Unknown
- ◯ N/A

What is the Enhanced Form date (date reviewed by DoH)?

_____

Has this person had a negative hepatitis C antibody test within the past 24 months?

- ◯ No
- ◯ Yes
- ◯ Unknown

Date of last negative test

_____

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Confirmation that this infection was notified previously Interstate and to the National Notifiable Diseases Surveillance System?	○ Yes, record as Previously Notified Interstate ○ No, Confirmation Status remains Confirmed

Has patient had any of the following risk exposures (please tick all options that apply for each risk exposure)

	Yes (within last 2 years)	Yes (over 2 years ago)	No	Unknown
Injecting drug use	○	○	○	○
Imprisonment	○	○	○	○
Sexual partner of opposite sex with HCV	○	○	○	○
Sexual partner of same sex with HCV	○	○	○	○
Household contact with HCV	○	○	○	○
Perinatal transmission	○	○	○	○
Tattoos	○	○	○	○
Acupuncture	○	○	○	○
Ear or body piercing	○	○	○	○
Occupational needlestick/biohazard injury in non- healthcare worker	○	○	○	○
Non-occupational needlestick/biohazard injury (other than IDU)	○	○	○	○

3. Patient information of Patient [patient_id]

Age	__________________________________
Gender	○ Male ○ Female ○ Other ○ Unknown

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In which LGA does the patient live?	◯ Break O'Day ◯ Brighton ◯ Burnie ◯ Central Highlands ◯ Central Coast ◯ Circular Head ◯ Clarence ◯ Derwent Valley ◯ Devonport ◯ Dorset ◯ Flinders ◯ George Town ◯ Glamorgan/Spring Bay ◯ Glenorchy ◯ Hobart ◯ Huon Valley ◯ Kentish ◯ King Island ◯ Kingborough ◯ Latrobe ◯ Launceston ◯ Meander Valley ◯ Northern Midlands ◯ Sorell ◯ Southern Midlands ◯ Tasman ◯ Waratah/Wynyard ◯ West Coast ◯ West Tamar ◯ Unknown
Has patient had previous HCV treatment?	◯ Yes ◯ No ◯ Unknown ◯ N/A
Previous HCV treatment outcomes	◯ Patient had a sustained virological response (SVR) >12 weeks post treatment ◯ Patient did not have a sustained virological response (SVR) >12 weeks post treatment ◯ Unknown

4. Contact with GP for this notification Please specify if any contact with GP. When: Intervention arm: 2 weeks - 3 months Control arm: 3 months (for intervention arm, information can be updated through 3 month period.)

Have you been able to contact the GP for this Notification?	◯ Yes ◯ No (Please use a 30-day period to try to contact GP)
How many call attempts prior to reaching GP for this Notification?	_____ (Please specify the total number. Leave blank if unknown.)
How many call attempts were made to reach GP for this Notification?	_____ (Please specify the total number. Leave blank if unknown.)

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For GPs in the Control arm: has GP returned Enhanced Form (CRF) and/or did you call?	☐ GP had filled in our form and sent back ☐ GP was called ☐ Other (specify) (Check all that apply.)
Other reason why enhanced form not returned	_____
What is the reason this GP cannot be contacted for this notification?	◯ GP is no longer working at the practice ◯ GP referred patient to specialist care ◯ GP declined to be contacted ◯ Practice no longer exists ◯ Unable to access contact details for the GP ◯ Other (specify)
Other (specify)	_____

5. Assistance required
Intervention arm only.

Please specify the assistance required by [gp_name] for this notification.

What kind of assistance does the GP need in managing Hepatitis C care/ what questions do they have?	☐ Level 1: Information on the virus ☐ Level 2: Further testing advice ☐ Level 2: Conducting pre-treatment work-up assessment ☐ Level 3: DAA prescription guidelines, including linkage to specialist consultation ☐ Level 3: Advising on conducting post-cure management including methods of follow-up to manage risks; including harm minimization, reducing re-infection risk, opioid substitution therapy ☐ Level 3: Linking/referral to resources for patients with cirrhosis or other concerns to specialist support for ongoing management ☐ Level 4: Direct patient contact ☐ Other (Check all that apply.)
Please specify "other"	_____

6. Calls and contact with GP or Patient
Intervention arm only.

Please specify the calls that you have had with this GP over the 3 month period. Check all that apply

You can update this information any time during the 3-month intervention period

	Call 1	Call 2	Call 3	Call 4	Call 5

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Choose moments of contact with GP or Patient	☐	☐	☐	☐	☐

Please specify the date of the first contact

_____

Please specify duration of first call in minutes

_____
(Please leave blank if unknown.)

Were prior call attempts made before successful contact?

◯ Yes
◯ No

Details of unsuccessful prior calls

_____

Was this call with the GP or the patient?

◯ GP
◯ Patient

Please specify the date of the second call

_____

Please specify duration of second call in minutes

_____
(Please leave blank if unknown.)

Were prior call attempts made before successful contact?

◯ Yes
◯ No

Details of unsuccessful prior calls

_____

Was this call with the GP or the patient?

◯ GP
◯ Patient

Please specify the date of call 3

_____

Were prior call attempts made before successful contact?

◯ Yes
◯ No

Details of unsuccessful prior calls

_____

Please specify duration of call 3 in minutes

_____
(Please leave blank if unknown.)

Was this call with the GP or the patient?

◯ GP
◯ Patient

Please specify the date of call 4

_____

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Were prior call attempts made before successful contact?	○ Yes ○ No
Details of unsuccessful prior calls	_____
Please specify duration call 4 in minutes	_____ (Please leave blank if unknown.)
Was this call with the GP or the patient?	○ GP ○ Patient
Please specify the date of the call 5	_____
Were prior call attempts made before successful contact?	○ Yes ○ No
Details of unsuccessful prior calls	_____
Please specify duration of call 5 in minutes	_____ (Please leave blank if unknown.)
Was this call with the GP or the patient?	○ GP ○ Patient
Document other modes of communication with GP if applicable e.g. sending GESA guidelines or other links.	_____

7. Level of assistance provided

Intervention arm only.

Please specify the level of assistance provided to GP [gp_name] for this notification at the end of 3-month period.

Has assistance been provided to GP?	○ yes ○ no
Level of assistance provided to GP [gp_name] for this Notification	☐ level 1: information ☐ level 2: testing, awareness, pre-treatment work-up ☐ level 3: DAA guidelines, treatment support, post-cure management, referral to specialist ☐ level 4: direct patient contact ☐ other (Check all that apply.)
Please specify 'other'.	_____

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During which call did you start the intervention?	○ call 1 ○ call 2 ○ call 3 ○ call 4 ○ call 5 ○ unknown
During the direct-patient call, what intervention has been done?	☐ Referral back to GP ☐ Referred to online resources ☐ Direct information to patient (Check all that apply.)
WARNING: This call has not been recorded above.	
Has GP finished the intervention? (i.e. all required assistance has been provided to GP)	○ Yes ○ No ○ Other (specify)
Other intervention outcomes?	_____
Why not?	○ could not reach GP ○ GP did not want to be called back again ○ other ○ patient is lost to follow up ○ unknown
During which call did you finish the intervention?	○ call 1 ○ call 2 ○ call 3 ○ call 4 ○ call 5 ○ unknown
WARNING: This call has not been recorded above.	

8. Outcomes

Intervention arm and Control arm.

Please specify the outcomes (testing and treating) after 3 months

Please provide the date of recording information on the outcomes	_____
Has RNA test been ordered yet?	○ Yes ○ No ○ Unknown ○ Yes, but by another GP ○ Yes, but by a specialist
What do you think is the number 1 barrier for not RNA testing this Notification?	○ Patient lost to follow up (no longer engaged in care at this clinic) ○ Patient needed to be referred to specialist ○ Patient refused to undergo puncture ○ Unsuccessful attempts at blood draw ○ Other (specify)

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Please specify other barrier for no RNA testing	_____
Have results come back yet?	◯ Yes ◯ No ◯ Unknown
What is RNA test date?	_____ (Note that for a repeat PCR the lab date is the same as the RNA date)
What was the result of the HCV RNA test	◯ Detected ◯ Not detected ◯ Indeterminate
Were appropriate pre-treatment work-up blood tests collected e.g. full blood count (platelet count), liver enzymes (AST)	◯ Yes ◯ No
What is the number 1 barrier for no pre-treatment work-up blood tests	◯ Patient is lost to follow-up ◯ Patient declined blood draw ◯ Patient was referred to a specialist ◯ Patient transferred to another practice ◯ Other (specify)
Other pre-treatment blood work up barriers	_____
Has GP written a DAA script for this notification?	◯ Yes ◯ No ◯ Unknown
What is the number 1 barrier for not writing a DAA script?	◯ Patient is lost to follow-up at the practice ◯ Patient has transferred to another practice ◯ Patient was transferred to a specialist ◯ Patient declined treatment ◯ Other (specifiy)
Other reason for no DAA script	_____
Has treatment already started?	◯ Yes ◯ No ◯ Unknown
What is the treatment start date?	_____
What do you think is the number 1 barrier for not treating this Notification?	◯ Patient lost to follow up ◯ Patient needed to be referred to specialist ◯ Patient refused treatment ◯ Other
Please specify other barrier for not treating	_____

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Consent for a future follow up call (to assess sustained virologic response)	○ Yes ○ No

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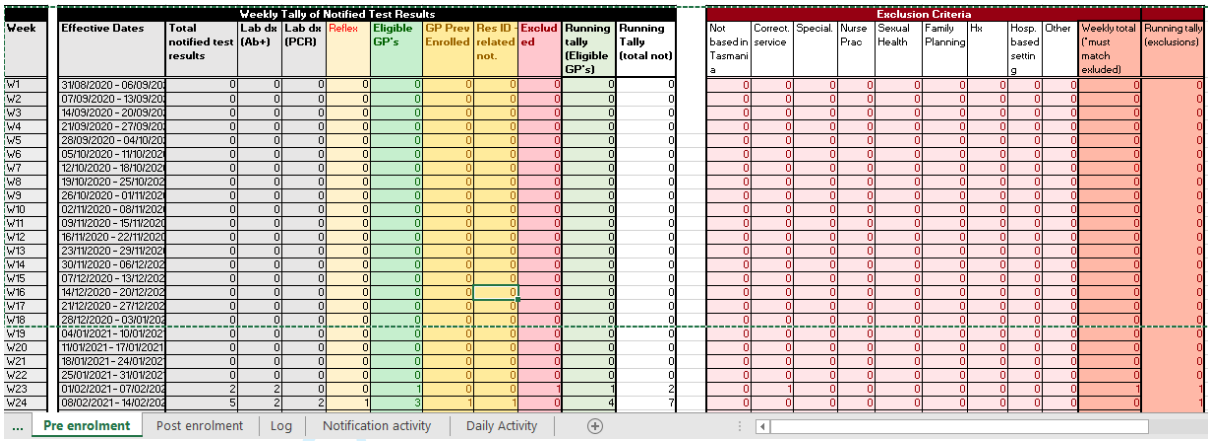
Appendix D: Screening Log



Week	Effective Dates	Weekly Tally of Notified Test Results: Total notified test results	Lab dx (Ab+)	Lab dx (PCR)	Reflex	Eligible GP's	GP Prev Enrolled	Res ID related not.	Excluded	Running tally (Eligible GP's)	Running Tally (total not)	Exclusion Criteria: Not based in Tasmania	Correct. service	Special.	Nurse Prac	Sexual Health	Family Planning	Hx	Hosp. based setting	Other	Weekly total (*must match exluded)	Running tally (exclusions)
W1	31/08/2020 - 06/09/20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W2	07/09/2020 - 13/09/20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W3	14/09/2020 - 20/09/20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W4	21/09/2020 - 27/09/20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W5	28/09/2020 - 04/10/20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W6	05/10/2020 - 11/10/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W7	12/10/2020 - 18/10/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W8	19/10/2020 - 25/10/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W9	26/10/2020 - 01/11/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W10	02/11/2020 - 08/11/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W11	09/11/2020 - 15/11/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W12	16/11/2020 - 22/11/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W13	23/11/2020 - 29/11/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W14	30/11/2020 - 06/12/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W15	07/12/2020 - 13/12/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W16	14/12/2020 - 20/12/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W17	21/12/2020 - 27/12/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W18	28/12/2020 - 03/01/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W19	04/01/2021 - 10/01/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W20	11/01/2021 - 17/01/2021	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W21	18/01/2021 - 24/01/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W22	25/01/2021 - 31/01/202	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W23	01/02/2021 - 07/02/20	2	2	0	0	1	0	0	1	1	2	0	1	0	0	0	0	0	0	0	1	1
W24	08/02/2021 - 14/02/20	5	2	2	1	3	0	1	0	4	7	0	0	0	0	0	0	0	0	0	0	1

... | Pre enrolment | Post enrolment | Log | Notification activity | Daily Activity

Appendix E: Sample size calculations

The sample size calculation is powered to cover a range of the most probable and realistic assumptions.

1. Treatment uptake in standard of care arm: Existing data estimates between 3-8% of people start therapy within three months (when our primary outcome will be assessed): data on national treatment uptake by specialists and general practitioners,[16] among people who inject drugs,[17] and in traditional referral to outpatient services all estimate treatment uptake of 8% or under at three months.[18] In this study, we will assume the higher (and therefore more conservative, biasing towards the null hypothesis) estimate of treatment uptake of 8% at three months in the control arm.

2. Treatment uptake in intervention arm: is estimated at 25% based on best estimates of intervention acceptance by GPs and follow up, RNA prevalence among those notified with HCV antibody, community treatment eligibility, and best estimate of intervention effect.

- Acceptance and participation of general practitioners is estimated at 90% at 3 months based on general practice acceptance of prescribing support (fewer than 10% of South Australian general practitioners declined SA Health support during remote follow up; unpublished data).

- RNA prevalence among those HCV-antibody positive has been measured 50-70% in surveillance data over the past 10 years.[19]

- Community treatment eligibility has been observed at 88% (10% cirrhosis, and 2% HIV or HBV coinfection or other serious comorbidities) in our Australian community treatment trials.[20]

- Intervention of primary care support is estimated to see 65% of eligible patients start on treatment at three months. We have informed this estimate based on pilot data from primary care support provided in Victorian models of support for general practitioners (91% treatment uptake among HIV-prescribers[21]; 74% treatment uptake in testing support models in community settings[22]; 71% follow up for treatment in a South Australian model of health department remote follow up, unpublished data). We have conservatively assumed a lower rate of treatment uptake among all eligible, viraemic patients of 65%.

Based on the most conservative of these assumptions, we estimate 25% (i.e., 0.90 x 0.50 x 0.88 x 0.65) of individuals in the intervention arm will commence treatment.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Reported on page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,14
	5b	Name and contact information for the trial sponsor	14
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4

	6b	Explanation for choice of comparators	3,5
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-7, Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8-9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-9

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8-9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9-10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	8-9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	14
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	9

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.