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*Published in:*  
Alimentary Pharmacology & Therapeutics

*DOI:*  
[10.1111/apt.16953](https://doi.org/10.1111/apt.16953)

*Publication date:*  
2022

*Licence:*  
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*Document Version*  
Publisher's PDF, also known as Version of record

[Link to publication in Discovery Research Portal](#)

### *Citation for published version (APA):*

Byrne, C. J., Radley, A., Inglis, S. K., Beer, L., Palmer, N., Duc Pham, M., Allardice, K., Wang, H., Robinson, E., Hermansson, M., Semizarov, D., Healy, B., Doyle, J. S., & Dillon, J. F. (2022). Reaching people receiving opioid agonist therapy at community pharmacies with hepatitis C virus: An international randomised controlled trial. *Alimentary Pharmacology & Therapeutics*, 55(12), 1512-1523. <https://doi.org/10.1111/apt.16953>

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# Reaching people receiving opioid agonist therapy at community pharmacies with hepatitis C virus: an international randomised controlled trial

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## Funding information

AbbVie LTD, Grant/Award Number: 811527

## Summary

**Background:** Conventional healthcare models struggle to engage those at risk of hepatitis C virus (HCV) infection. This international study evaluated point-of-care (PoC) HCV RNA diagnostic outreach and direct-acting antiviral (DAA) treatment for individuals receiving opioid agonist therapy (OAT) in community pharmacies.

**Aims:** We assessed the effectiveness of a roving nurse-led pathway offering PoC HCV RNA testing to OAT clients in community pharmacies relative to conventional care.

**Methods:** Pharmacies in Scotland, Wales, and Australia were randomised to provide PoC HCV RNA testing or conventional referral. Pharmacists directed OAT clients to on-site nurses (intervention) or local clinics (control). Infected participants were treated with DAAs, alongside OAT. Primary outcome was the number of participants with sustained virologic response at 12 weeks (SVR) and analysed using mixed effects logistic regression in the intention-to-treat (ITT) population.

**Results:** Forty pharmacies were randomised. The ITT population contained 1410 OAT clients. In the conventional arm ( $n = 648$ ), 62 (10%) agreed to testing, 17 (27%) were tested, 6 (35%) were positive and 5 (83%) initiated treatment. In the intervention arm ( $n = 762$ ), 148 (19%) agreed to testing, 144 (97%) were tested, 23 (16%) were positive and 22 (96%) initiated treatment. SVR was obtained by 2 (40%; conventional) and 18 (82%; intervention). Intervention arm participants had higher odds of testing, OR 16.95 (7.07–40.64,  $p < 0.001$ ); treatment, OR 4.29 (1.43–12.92,  $p = 0.010$ ); and SVR, OR 8.64 (1.82–40.91,  $p = 0.007$ ).

**Conclusions:** Nurse-led PoC diagnosis in pharmacies made HCV care more accessible for OAT clients relative to conventional care. However, strategies to improve testing uptake are required. Trial registration: NCT03935906.

The Handling Editor for this article was Geoffrey Dusheiko, and it was accepted for publication after full peer-review.

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## 1 | INTRODUCTION

Hepatitis c virus (HCV) is a blood-borne virus typically spread through percutaneous exposure to infected blood. Previously considered challenging to treat, the arrival of direct-acting antiviral (DAA) treatment changed the therapeutic landscape to such an extent that elimination of HCV as a public health threat became a feasible goal.<sup>1</sup> To that end, the World Health Organization (WHO) released its first Global Health Sector strategy which called for the elimination of HCV through novel strategic approaches underpinned by diagnostic advances and highly effective DAAs.<sup>2</sup> To facilitate HCV elimination, new strategic approaches to improve screening and linkage to care for affected groups—fundamental requirements of WHO elimination targets—are required.<sup>3</sup> One of the priority affected groups in high-income countries are current or previous people who inject drugs (PWID), the population of interest in this study.

Globally, approximately half of PWID are estimated to have been exposed to HCV (anti-HCV positive). Relevant to this study, national and sub-national estimates indicate that proportions of PWID affected by HCV in Scotland is 52.2% (95% CI 45.5–58.5), in Wales 26.8% (95% CI 23.4–30.4); and in Australia is 53.5% (95% CI 50.2–56.9).<sup>4</sup> Recent studies have found low rates of confirmatory RNA testing and transition to treatment among HCV antibody positive PWID, and high levels of chronic HCV infection.<sup>5–7</sup> Following periods of injection drug use (IDU), many PWID are engaged on a managed programme of opioid agonist therapy (OAT) in order to reduce their substance use. While in receipt of OAT, it was previously reported that approximately 43% in this group will experience chronic or relapsing opioid substance use.<sup>8</sup> Given the high prevalence of HCV among PWID, low testing and treatment transition rates, and the high continued risk of infection among those receiving OAT, tailored initiatives to improve diagnosis of HCV and uptake of treatment are essential.<sup>9</sup>

Conventional care in the United Kingdom and Australia includes regularly offering HCV testing to those with current or previous IDU, for example through drug treatment services or general practitioners. A positive HCV result will trigger onward referral to a treatment pathway often fixed around a secondary-care context. This system causes unnecessary patient attrition, which has led to decentralisation of HCV care tasks out of specialist secondary settings into non-specialist community settings to improve linkage to care.<sup>10</sup> Previous studies have shown positive results with respect to feasibility and acceptability of pharmacists offering HCV testing and treatment with DAAs, as well as the ability to improve uptake of testing and treatment in this context.<sup>11–13</sup> However, for more remote pharmacies with relatively fewer OAT clients, this model may not be resource efficient, as a nurse could feasibly have offered point-of-care (PoC) HCV tests to the whole cohort of clients in a cluster of pharmacies in the time it takes to train pharmacy staff adequately.

Accordingly, this study aimed to assess the effectiveness of a roving nurse-led model which offered PoC HCV RNA testing plus DAA treatment to OAT clients in community pharmacies, while leveraging the skills of community pharmacists to encourage testing

and support treatment adherence for HCV-positive individuals. We aimed to assess testing uptake, treatment initiation and completion, and levels of cure, for a population of OAT clients at risk of HCV infection.

## 2 | METHODS

### 2.1 | Study design and participants

This is an international, multi-centre, cluster-randomised trial of outreach PoC HCV diagnosis and DAA treatment versus conventional care for clients in receipt of OAT at community pharmacies. The trial was run in Scotland (UK), Wales (UK) and Australia. The trial was conducted in 40 pharmacies which provided OAT dispensing services routinely.

Eligible community pharmacies received study training and literature to facilitate opportunistic HCV discussion with OAT clients and onward referral. Pharmacies received equivalent training and resources (training slides; posters advertising testing and treatment; flowcharts explaining trial activities; facilitated discussion sheets; participant information leaflets) in both arms of the trial, with the exception that, in the control arm, pharmacists were instructed to direct clients to conventional testing venues rather than study nurse(s). All OAT clients at participating pharmacies were included in the trial population, as they represented the cohort at risk of HCV infection. PoC testing was administered in the intervention arm using the Genedrive Diagnostics® instrument, which is a compact qualitative HCV RNA testing device which provides a detected/not detected result in 90 min using 30 µl of sample.<sup>14</sup> Nurses were trained in its use by the manufacturer prior to study initiation, with ongoing support when required. There was one dedicated study nurse per hub for the 20 intervention sites (six in Scotland, seven each in Wales and Australia), responsible for study conduct and clinical contacts, with ad-hoc additional nursing support when available. Nursing capacity in the conventional care arm fluctuated in line with standard service provision.

Individuals were eligible for HCV treatment if they were HCV positive; ≥18 years of age; a previous or current injection substance user; in receipt of OAT for 12 weeks prior to participation; were naïve to glecaprevir/pibrentasvir; and able to understand the study and provide informed consent. They were ineligible if they had current HIV or hepatitis B virus infection; prior treatment with glecaprevir/pibrentasvir; were pregnant or planning to become pregnant; were taking contra-indicated concomitant medication; decompensated liver disease; sensitivity to excipients of glecaprevir/pibrentasvir; or other uncontrolled medical conditions which deemed them unsuitable in the view of the investigators.

### 2.2 | Randomisation and masking

Eligible pharmacies functioned as the unit of randomisation. Prior to participant recruitment, pharmacies were randomised 1:1 on a

per-hub basis (Scotland, Wales, Australia) to the intervention or the control pathway. Randomisation was on a per-hub basis to ensure equal distribution of intervention and control sites in each country. Pharmacies were allocated a reference number and randomisation was performed by Tayside Clinical Trials Unit (TCTU) staff using [www.graphpad.com](http://www.graphpad.com) to generate randomly allocated blocks. Masking of site allocation was not performed; pharmacists and participants were aware to which arm of the study they were assigned. This was necessary in order to ensure appropriate functioning of testing and treatment within the pathways.

## 2.3 | Procedures

Prior to commencing recruitment, pharmacists received study training and materials to support opportunistic discussion of HCV and referral to testing with their OAT clients. Study nursing staff were trained on study protocols and had appropriate training in good clinical practice.

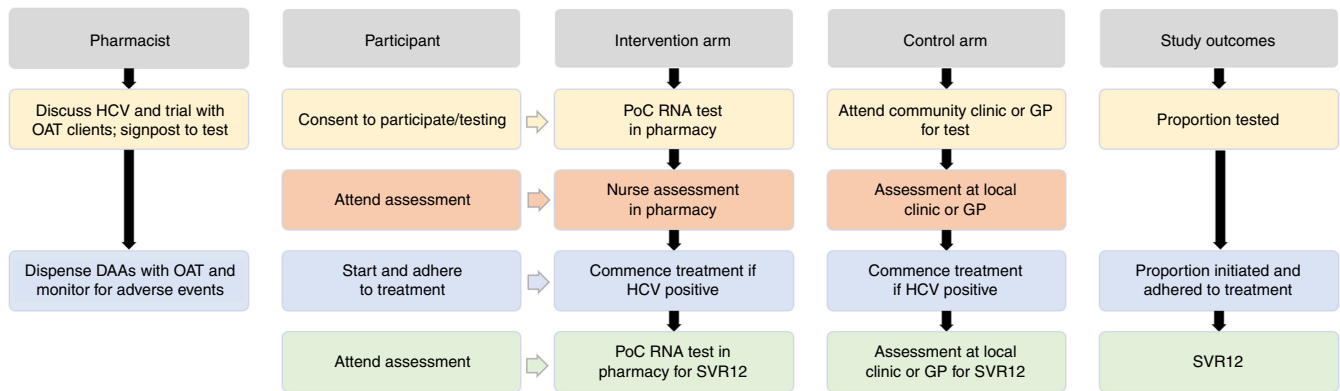
In the intervention pathway, pharmacists discussed HCV with their OAT clients immediately prior to opening to patient recruitment. OAT clients were informed when outreach nurses would be offering testing in the pharmacy. Nurses typically attended pharmacies for 1 week to screen OAT clients, with ad-hoc visits for subsequent study appointments or to test those who were interested in testing but not screened in the initial visit. Nurses obtained informed consent from interested OAT clients and, for those who agreed to participate, whole blood samples were obtained using conventional venepuncture. HCV RNA testing was performed by study nurses in pharmacy consultation spaces, and additional bloods were taken for full blood count, urea and electrolytes, liver function testing, including markers of liver fibrosis, and viral parameters in line with eligibility criteria. Baseline samples were stored in a  $-80^{\circ}\text{C}$  freezer for resistance assessment in the event of non-response despite treatment adherence.

Typically, participants did not wait for their result on the day of their test. Therefore, at a subsequent visit to pharmacies, when secondary bloodwork confirming eligibility for treatment was also available, HCV-positive participants were assessed for DAA treatment by study nurses, including assessments for gastrointestinal, coronary, haematologic and respiratory co-morbidities, and completed study questionnaires covering demographics, injecting behaviour and quality of life (EQ-5D-5L). HCV-negative participants had their PoC HCV results confirmed at this visit, by telephone, or by letter routed through their pharmacist, following secondary confirmation from laboratory testing. Any participants who tested HCV negative on the PoC device, but positive on the secondary confirmatory test, were assessed for treatment. This occurred if their viral load was below the limit of detection of the PoC device (2362 IU/ml).<sup>14</sup> DAA treatment was arranged by nursing staff in UK sites, under provision of a patient group direction (PGD), and the clinical investigator in Australia.<sup>15</sup> In UK sites, medication was arranged by study nurses, aligned to the protocol, and within the framework

of the PGD, depending on participants' treatment history, secondary bloodwork, and, if treatment experienced, genotype. For more complex cases (e.g. unknown treatment history, previously treated with DAAs), multi-disciplinary team and clinician consultation was undertaken. All Australian treatment was prescribed by a qualified physician. Once treatment was commenced, the nurse next visited pharmacies to provide PoC testing for sustained virologic response 12 weeks post-treatment (SVR12) and collect post-treatment questionnaire data on injecting behaviour and quality of life. Consequent to COVID-19 (C-19), some in-person follow-up tests by nursing staff were not feasible, and participants were directed to tertiary centres for SVR12 testing. Where possible in these cases, questionnaire items were completed by phone.

In the conventional pathway, similar to intervention sites, pharmacists opportunistically discussed HCV with their OAT clients using standard health service HCV literature and provided study information. Clients were signposted to community outreach clinics for HCV testing in UK sites, and to their general practitioners (GP) in Australian sites. This reflects conventional care in each country. In UK sites, participants provided informed consent to participate at the outreach clinic. In Australia, to secure permission for follow-up after attending GP services, participants were consented by community pharmacists prior to being signposted to testing, nurses then contacted participants by phone to ascertain testing status. HCV-positive participants completed the same pretreatment questionnaire data, including comorbidity assessments, as those in intervention arm, either at the clinic (UK) or the pharmacy (Australia). DAA treatment provision and on-treatment follow-up occurred in line with standard care protocols. However, for study purposes, those who initiated treatment next attended the clinic (UK sites) or their GP (Australia) for SVR12 testing. Post-treatment questionnaire data were collected in clinics (UK) and pharmacies or, due to C-19, by telephone (Australia). An outline of the pathways is shown in [Figure 1](#).

HCV testing was provided at zero cost to participants in both arms. Costs were covered either directly from the study budget, or indirectly via NHS costs support from the National Institute for Health Research (NIHR) Clinical Research Network.<sup>16</sup> All HCV-positive participants received 100mg glecaprevir/40mg pibrentasvir film-coated tablets, except Australian control-arm participants who could be prescribed any DAA in line with Pharmaceutical Benefits Scheme (PBS) guidelines.<sup>17</sup> For equity with other hubs, PBS co-payments, where applicable, were reimbursed by the trial. DAAs were dispensed by community pharmacists in line with participants' regular OAT dose, which included a mixture of daily-observed and take-home schedules, depending on the individual. Treatment duration with 100mg glecaprevir/40mg pibrentasvir (8, 12 or 16 weeks) was determined by the outcome of baseline blood testing and individuals' specific HCV treatment history. Participants with AST to platelet ratio index (APRI) score of  $\leq 1$  received 8 weeks, while those with APRI  $> 1$  received a Fibrosan. There was no change to treatment where results were consistent with portal fibrosis (F) F0–F3; if results were consistent with advanced liver disease (F4;  $> 11$  kPa), treatment was extended. More detail is available in the published



**FIGURE 1** Overview of intervention and control pathways with related study outcomes. HCV, hepatitis c virus; OAT, opioid agonist therapy; DAA, direct-acting antiviral; PoC, point of care; RNA, ribonucleic acid; SVR, sustained virologic response

protocol.<sup>18</sup> Glecaprevir/pibrentasvir was provided free of charge by AbbVie for the study. Community pharmacists recorded provision of DAAs on a dispensing log for each participant, in order to estimate treatment adherence. Adverse events were monitored during study visits by nursing staff, and community pharmacists reported any reported side effects to the study team for follow-up.

The study received favourable ethical opinion from East of Scotland Research Ethics committee for UK sites (19/ES/0025) and the Alfred Hospital Ethics Committee (149/19). Sponsorship in the UK was provided via a joint agreement between Tayside Health Board and the University of Dundee; for Australian sites, it was provided by the Alfred Hospital. Overall administration of the trial was provided by TCTU, a UK Clinical Research Collaboration (UKCRC)-registered trials unit. The trial protocol has been previously published and the study is registered on [clinicaltrials.gov](https://clinicaltrials.gov), NCT03935906.<sup>18</sup>

## 2.4 | Outcomes

The primary outcome for the study was the proportion of participants with SVR12 in each arm and was analysed in the intention-to-treat (ITT) population. Secondary outcomes were proportion of participants with SVR12 in each arm in the known HCV-infected population (modified intention-to-treat, mITT), and in both the ITT and mITT populations: proportions of individuals tested for HCV per arm; proportion of individuals who initiated treatment per arm; proportion of individuals who completed HCV treatment per arm. Finally, an assessment of the proportion of participants who required extended treatment durations (>8 weeks) was undertaken. A cost-effectiveness analysis will be conducted as part of a wider ongoing monitoring study and is not reported here.<sup>19</sup>

## 2.5 | Statistical analysis

Statistical analysis was conducted in line with a pre-planned statistical analysis plan. The primary outcome of SVR12 was assessed as a binary outcome using logistic regression modelling in Stata IC 16.

The primary analysis was performed at the patient level in the ITT population. This ITT analysis included the total number of OAT clients in each arm of the study as this represented the population at risk of HCV infection who could potentially be tested through the study. Any participants who were missing SVR12 for any reason were assumed to be treatment failures and analysed accordingly, so there were no missing data in the primary outcome. As the study was cluster randomised, mixed-effects logistic regression modelling was used with a parameter indicating the trial arm, and a random parameter to account for within-cluster correlation.

Secondary outcomes (proportions tested, initiated treatment, and completed treatment) were analysed by the same method in the ITT group. This secondary analysis was also planned for the mITT group, comprised of all HCV-positive participants, with adjustment by genotype and prior treatment exposure, but this was not feasible due to the lower-than-expected quantity of HCV-positive participants. Instead, figures illustrating differences are provided in File S1 (pages 1-2), and proportions of participants at key steps in the cascade of care are reported (Figure 3). The ITT analysis was adjusted post-hoc for pharmacy-level factors: resource deprivation and size of pharmacy. *P* values  $\leq 0.05$  were assumed to be significant. A further secondary outcome, reported descriptively, is the number of persons who required extended treatment and the reasons for this.

The diagnosed population SVR12 level was calculated as the number of participants with SVR12 as a proportion of observed HCV-infected participants. Additional cure evaluations were calculated as proportions of the estimated infected population based on published evidence and the empirical rate observed in the trial. Differences in time from screening to treatment were assessed with descriptive statistics and compared using the Mann-Whitney U test. Sample size calculations have been reported previously; in summary, the trial required approximately 140 HCV-positive participants.<sup>18</sup>

## 2.6 | Role of funding source

AbbVie were involved in a collaborative, iterative process to develop the study protocol alongside the study investigators as part of the

AbbVie Investigator Initiated Scheme and provided the funding for this study. AbbVie provided input to the protocol with regards to safety measures and reporting; the participant journey; and HCV medication guidance. AbbVie representatives provided feedback and input to this manuscript but were independent of the data analysis.

### 3 | RESULTS

Between 8 October 2019 and 14 January 2021, 1410 OAT clients attended the 40 pharmacies that were participating in the trial. The pharmacies were randomised equally to each arm of the study (Figure 2).

Patient demographic characteristics are outlined in Table 1, with detailed characteristics only available for those who agreed to treatment. In summary, the majority of participants were male and median age was over 40 years. Most reported recent depression and anxiety at baseline and were stably housed but unemployed. The most common income type reported was receipt of government allowance/benefits.

Data on substance use and well-being parameters are tabulated in File S1 (page 3). The median age of first IDU was 17 years, with a near even split of participants reporting IDU in the 6 months prior to treatment. Of those that had injected recently, the highest reported frequency was one to three times per month. When asked at follow-up about injecting since finishing treatment, most reported they had not, with one quarter of participants indicating they had—frequency varied between individuals. Median EQ-5D-5L score at baseline was 62.50, and at SVR12 was 65.<sup>20</sup>

Clinical information for those who initiated treatment ( $n = 27$ ) is outlined in Table 2. The majority of treated participants were HCV genotype 3; were treatment naïve; and non-cirrhotic. Of the five individuals who had extended treatment durations, most were due to cirrhosis, with one consequent to prior HCV treatment experience. There were few participants who reported medical co-morbidities. The average number of days from screening to treatment initiation was lower for the intervention (mean 18.0, SD 13.7) than the control arm (mean 63, SD 81.0), but differences in distribution were not significant ( $p = 0.928$ ). This is likely consequent to the small sample of treated cases in the control arm limiting the sensitivity of the test ( $n = 5$ ).

Pharmacy characteristics were broadly similar in UK hubs, but slightly more varied in Australia. These are outlined in full in File S1 (pages 4–5). All pharmacies in UK sites were classified as small, whereas Australian pharmacies were an even mix of small, medium and large. In Scotland and Wales, most pharmacies were located in areas of lowest resource, whereas in Australia pharmacies tended to be located in areas of mid-to-highest resource.

In the ITT analysis (Figure 2) for primary outcomes, 144 participants were tested for HCV in the intervention arm, compared to 17 in the control arm (odds ratio [OR] 16.95, 95% CI 7.07–40.64,  $p < 0.0001$ ); 22 participants in the intervention pathway initiated

treatment, compared to five in the control pathway (OR 4.29, 95% CI 1.43–12.92,  $p = 0.010$ ); and 18 participants completed treatment in the intervention arm, compared to 4 in the control arm (OR 4.53, 95% CI 1.39–14.71,  $p = 0.012$ ). Eighteen of 762 participants in the intervention arm obtained SVR12 compared to 2 of 648 participants in the conventional arm (OR 8.64, 95% CI 1.82–40.91,  $p = 0.007$ ). In intervention group, there were two with detectable RNA at SVR12, with the remainder lost to follow-up (LTFU); in the control group there were zero with detectable RNA at SVR12, and 2 LTFU. Estimated cure rates are reported along with ITT analytical outcomes in Table 3.

When adjusted (File S1, page 6) for resource deprivation and pharmacy size, those in medium (OR 0.10, 95% CI 0.02–0.42,  $p = 0.002$ ) and large-sized (OR 0.23, 95% CI 0.10–0.55,  $p = 0.001$ ) pharmacies had reduced odds of receiving a HCV test compared to those in smaller premises. These parameters were not significant with respect to initiating treatment. Those in mid-resource areas had higher odds of completing treatment (OR 4.08, 95% CI 1.36–12.17,  $p = 0.012$ ) and obtaining SVR12 (OR 3.75, 95% CI 1.20–11.73,  $p = 0.023$ ) compared to those in the most and least resourced neighbourhoods. Modelling pharmacy size for treatment completion and SVR12 was not feasible in adjusted analyses.

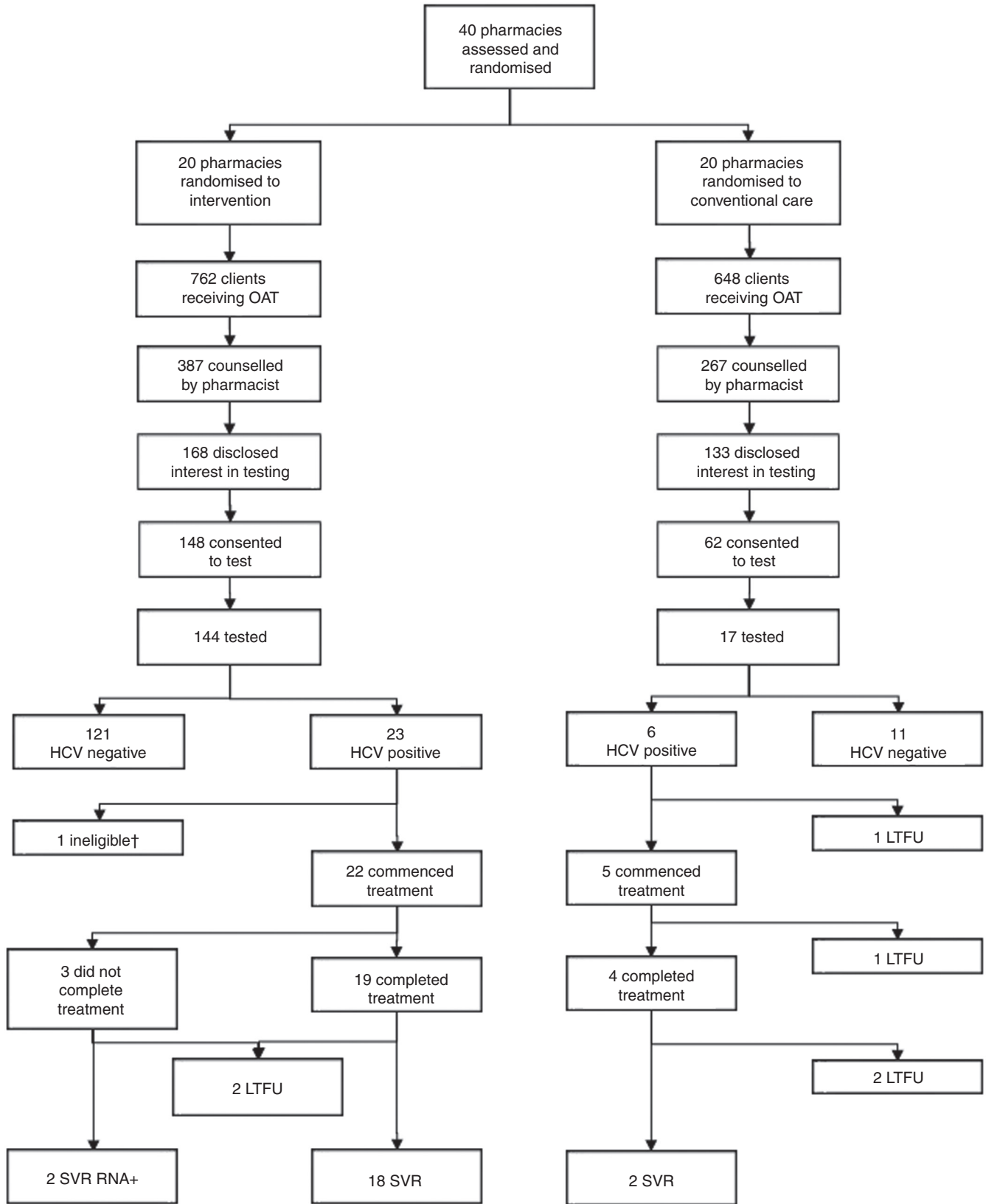
A post-hoc descriptive analysis of key stages of HCV care was performed (Figure 3). The intervention pathway outperformed conventional care in linkage to testing, treatment initiation, completion and SVR12. Raw data are tabulated in File S1 (page 7).

Importantly, over half of all OAT clients in intervention sites received HCV counselling from their pharmacist, compared to less than half in conventional care sites (File S1, page 8). In all sites, the majority of clients who were counselled on the risks of HCV, but not interested in HCV testing, did not give a specific reason. Among those who disclosed a reason, receiving a recent HCV test was most common, followed by recent HCV treatment (conventional arm), and not having time (intervention arm).

During the study, seven adverse events (AE) were recorded, and one serious adverse event (SAE) was recorded. None were related to study participation. These are fully tabulated in File S1 (page 9).

### 4 | DISCUSSION

The study findings suggest using a roving nurse-led model to integrate PoC diagnosis for HCV into community pharmacies can increase the number of patients who obtain a cure for their HCV infection, compared to conventional care. The results also indicate that this model increases the proportion of patients who access HCV testing, initiate and complete DAA treatment, if required. Furthermore, leveraging the existing patient-provider relationship in community pharmacies was a useful strategy to drive engagement of OAT clients and maintain sufficient compliance with DAA treatment. Cure rates, as proportions of the estimated infected population, were superior to conventional care, as was speed of transition from screening to treatment. The results align with a previous randomised controlled trial exploring community pharmacies as



**FIGURE 2** Profile of the trial structure, population, and outcomes. Abbreviations: HCV, hepatitis C virus; LTFU, lost to follow-up; OAT, opioid agonist therapy; RNA+, ribonucleic acid positive; SVR, sustained virologic response. †Individual ineligible for community treatment (Australia) due to prior treatment failure

TABLE 1 Participant demographic parameters at baseline

Parameter	Treatment initiators (n = 27)	Consented population (n = 210)
Gender, n (%)		
Male	17 (62.96)	137 (65.24)
Female	10 (37.04)	73 (34.76)
Age, median (IQR)	43 (15)	42 (13)
Depression, n (%)		
Yes, in last 6 months	18 (66.67)	NC
No, not in last 6 months	9 (33.33)	
Anxiety, n (%)		
Yes, in last 6 months	19 (70.37)	NC
No, not in last 6 months	8 (29.63)	
Accommodation, n (%)		
Owned/renting	15 (55.56)	NC
Network flat	5 (18.52)	
Sofa surfing	2 (7.41)	
Other	5 (18.52)	
Employment, n (%)		
Not employed	20 (74.07)	NC
Full-time work	1 (3.70)	
Part-time work	4 (14.81)	
Student	1 (3.70)	
Other	1 (3.70)	
Primary income, n (%)		
Regular wage	3 (11.1)	NC
Government allowance	22 (81.48)	
Other	2 (7.41)	

Abbreviations: IQR, inter-quartile range; NC, not collected.

focal points for HCV testing and treatment in Scotland.<sup>13</sup> In that study, pharmacists performed dried blood spot (DBS) testing with OAT clients and cure rates in the intervention arm were more than double those achieved by conventional care. However, while that study focussed on pharmacies with a large number of OAT clients, our trial concentrated on smaller sites, where training pharmacy staff would not have been resource efficient. Our study also extends the evidence base to an international context, suggesting the model is deliverable in diverse health systems. However, sustained feasibility in a given health system will also be determined by external factors, such as financial aspects (e.g. insurance coverage of HCV testing and treatment); policies that govern prescribing and delivery of DAAs; and logistical considerations consequent to such policies.<sup>24-26</sup> Some places continue restricting access to DAAs based on patient behaviour, such as ongoing substance use, or requirements for specialist consultation prior to treatment which are not aligned with prevailing recommendations.<sup>25-27</sup> We hope that this study can reiterate the necessity for zero-cost low-threshold access to HCV testing and treatment in non-specialist settings for PWID, and contribute to changing such policies.

A recent systematic review and meta-analysis of DAA treatment and SVR among people who inject (or use) drugs suggested that,

among those in receipt of OAT who were treated with DAAs for HCV, 88–91% obtained SVR in ITT analysis.<sup>28,29</sup> This is higher than the proportion in the intervention arm of this trial; we suggest this is predominantly due to LTFU or non-adherence rather than treatment failure, as these were the primary reasons for not achieving SVR12 across both pathways. The C-19 pandemic made follow-up of participants challenging to facilitate. Of the two participants with detectable RNA at SVR12 in the intervention arm, neither individual had adhered to treatment as prescribed. Of those who completed treatment in the intervention arm, SVR12 was 95% (Table S5), underlining the importance of adequate compliance with DAAs in achieving cure. Another systematic review, previously suggested that co-locating HCV care in community services is feasible, and can deliver increased uptake of DAA treatment, with SVR proportions similar to secondary care.<sup>30</sup> Results from this trial complement that evidence, and also suggest that use of innovative PoC technology is a feasible component of such integration into primary care environments, thereby helping to close the current gap in HCV diagnosis and linkage to care.<sup>9</sup> A relevant observation from this study to the decentralisation of HCV care is the low level of co-morbidity, liver cirrhosis and AEs in the population, suggesting only a minority



TABLE 2 Clinical parameters for treatment initiators (n = 27)

Parameter	n (%)
HCV genotype	
1	11 (40.74)
2	1 (3.70)
3	15 (55.56)
DAA prescribed	
100 mg glecaprevir/40 mg pibrentasvir	25 (92.59)
400 mg sofosbuvir/100 mg velpatasvir	2 (7.41)
Previous treatment	
No	21 (77.78)
Yes	6 (22.22)
Previous treatment type	
Peg-IFN	3 (50.0)
DAA (not Gle/Pib)	2 (33.3)
Peg-IFN and DAA (not Gle/Pib)	1 (16.7)
FIB-4 score	
<1.45	17 (62.96)
1.46–3.24	5 (18.52)
>3.25	5 (18.52)
AST:ALT ratio	
<1	18 (66.6)
>1	9 (33.3)
APRI score	
<1	17 (62.96)
>1	10 (37.03)
Transient elastography (kPa) <sup>a</sup>	
0–10.9	4 (50.0)
≥11	4 (50.0)
Medical co-morbidities	
No	18 (66.6)
Yes	9 (33.3)
Cirrhosis <sup>b</sup>	
No	21 (77.8)
Yes	6 (22.2)
Extended treatment prescribed <sup>c</sup>	
No	22 (81.48)
Yes	5 (18.51)
Extended treatment reason	
Cirrhosis	4 (75.00)
Previous HCV treatment	1 (25.00)
Prescription duration (weeks)	
8	20 (74.07)
12	6 (22.22)
16	1 (3.70)

Abbreviations: ALT, alanine transaminase; APRI, aspartate transaminase to platelet ratio index; AST, aspartate transaminase; DAA, direct-acting antiviral; FIB-4, fibrosis 4; Gle/Pib, 100 mg glecaprevir/40 mg pibrentasvir; HCV, hepatitis C virus; Peg-IFN, pegylated interferon.

<sup>a</sup>Performed using Fibroscan®. Ten participants had APRI scores which necessitated transient elastography. However, only eight received it due to logistical challenges.

<sup>b</sup>Defined as Fibroscan result ≥11.00 kPa.

<sup>c</sup>Defined as >8 weeks duration.

of cases among OAT clients in community pharmacies require extended treatment or specialist review. Leveraging nurses to lead decentralisation of HCV care has been shown to be highly effective compared to specialist services in populations treated with DAAs, and our findings complement this research.<sup>10</sup>

The high proportions of depression, anxiety, unemployment and socio-economic disadvantage among those participating in this trial aligns with previous evidence suggesting such disadvantage is associated with HCV infection.<sup>31</sup> Reports have suggested that those living in economic or socially disadvantaged circumstances are less able to navigate healthcare through conventional means,<sup>32</sup> for example, complex secondary care referral environments, and the control arm of the trial illustrates this. The model of care trialled in this study overcomes this barrier by bringing testing and treatment to a familiar and safe environment, where routine attendance by patients offers frequent opportunities to engage in HCV care. The intervention pathway also minimised other identified barriers (such as: geographic access to hospitals; stigma and discrimination)<sup>33</sup> by integrating into local community pharmacies and leveraging pharmacists' existing relationships with OAT clients to educate on HCV, signpost to testing and support treatment. The benefits of this convenience feature of the pathway are clear in our results, with those in the intervention arm being substantially more likely to receive a test in the trial and have improved outcomes throughout the care journey.

Despite this, overall testing uptake was somewhat lower than anticipated in intervention sites. Improving testing uptake in this population is crucial to achieving and maintaining HCV elimination. A recent systematic review identified pretest counselling, facilitated referral and non-invasive liver disease assessment—all undertaken in this trial—as key interventions to enhance testing uptake among PWID.<sup>34</sup> Therefore, based on our results, further work is required to identify appropriate diagnostic strategies. Among those who were not agreeable to testing, most did not disclose a reason, which makes future intervention design challenging. HCV testing for this study necessitated venepuncture, which may have disincentivised engagement. It may be that simpler non-invasive sampling methods, such as DBS—which multiple studies have implemented successfully in community settings<sup>34</sup>—are preferable. However, this would not give actionable same-day results. Alternatively, other PoC RNA devices which utilise capillary sampling for RNA testing may improve uptake.

Furthermore, although the vast majority of clients disclosing an interest in testing in intervention sites went on to receive a test, a substantial minority (49%, File S1, page 8) did not receive HCV counselling from their pharmacist and the associated testing referral. The C-19 pandemic commenced soon after the trial began and impacted pharmacist workload and patient interaction substantially. OAT dispensing patterns were changed to increase 'take-home' provision and reduce face-to-face and store traffic interaction considerably.<sup>35</sup> Recent data suggest the pandemic led to wider reductions in HCV testing globally.<sup>36</sup> Accordingly, we would suggest that HCV counselling and testing uptake would have been greater in the absence of the pandemic. A qualitative sub-study is ongoing to document pharmacists experience of delivering this intervention, and

TABLE 3 Outcomes of primary, secondary analyses and post-hoc estimates, in the intention-to-treat population (n = 1410)

Outcome	Intervention arm (n = 762)	Conventional arm (n = 648)	OR (95% CI)	p
HCV tested	144	17	16.95 (7.07–40.64)	<0.0001
Initiated treatment	22	5	4.29 (1.43–12.92)	0.010
Completed treatment	19	4	4.53 (1.39–14.71)	0.012
SVR12	18 (2%)	2 (0.3%)	8.64 (1.82–40.91)	0.007
Diagnosed population (cure rate)	23 (78%)	6 (33%)	–	–
Estimated infected population <sup>a</sup> (cure rate)	137 (13%)	117 (2%)	–	–
Estimated infected population <sup>b</sup> (cure rate)	168 (11%)	143 (1%)	–	–

Abbreviations: HCV, hepatitis C virus; OR, odds ratio; SVR, sustained virologic response.

<sup>a</sup>Estimated infected population calculated at a rate of 18%, in line with overall proportion of those tested in both arms of the study who were RNA positive.

<sup>b</sup>Infected population approximated at a rate of 24%, in line with available surveillance estimates.<sup>21–23</sup>

future studies might consider strategies to increase the fidelity of pharmacist-delivered HCV counselling.

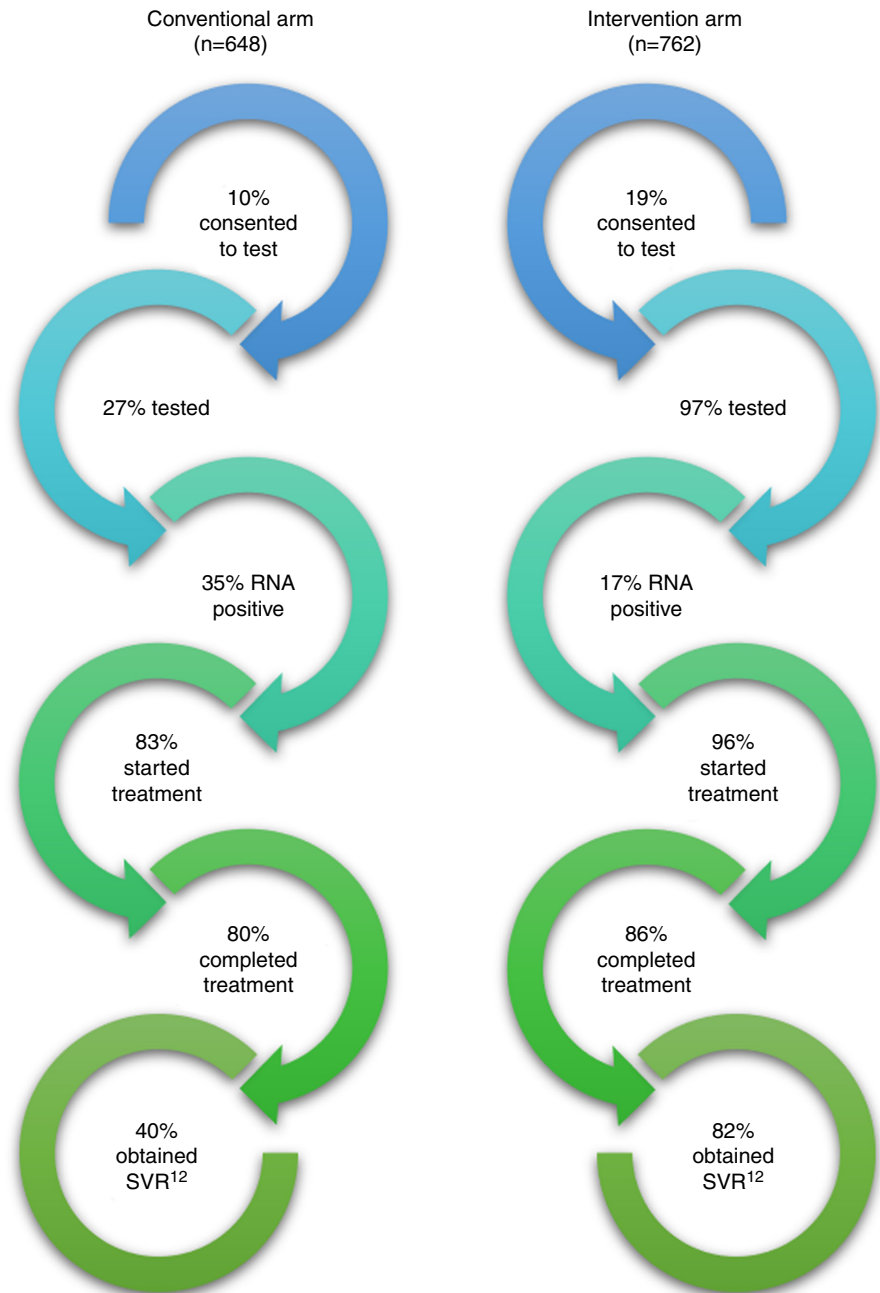
The secondary adjusted ITT analysis (File S1, page 6) implied that those in areas of middle resource were more likely to complete treatment and obtain SVR12 compared to those in areas of most and least resource. There was an even split of treatment completion across mid and most resourced areas in the control arm, with none in the least resourced; similarly, there was a relatively even distribution of completion across all resource indices in the intervention arm. Both cures in the control arm originated from pharmacies in mid-resource areas, with an even distribution across resource indices in the intervention arm. We would suggest the statistical associations are a consequence of the relatively few participants tested and treated in the least resourced areas in the control arm. More pertinently, the absolute numbers used for these analyses suggest the intervention pathway functioned more effectively in lower resource areas than conventional care did, particularly as the highest proportion of tests performed were in these areas in the intervention arm, as opposed to mid-resource areas in the control arm. This aligns with previous research suggesting that OAT clients in outlying areas or communities of low resource struggle to access HCV care in conventional primary healthcare settings.<sup>37</sup> The outreach model trialled in this study may provide an effective solution to this. With respect to pharmacy size, it may be that pharmacies with fewer OAT clients facilitate engagement by pharmacists and nurses, however, the vast majority of pharmacies in the study were classified as small, so the association may be spurious.

There was no meaningful change in median EQ-5D scores from baseline to follow-up (62.50 v 65.00) among those who initiated treatment and completed the questionnaire data. Previous Scottish research has shown that awareness of one's chronic HCV status is associated with reduced health-related quality of life (QoL) among PWID.<sup>38</sup> In that work, median EQ-5D scores for chronically infected PWID were comparable to those found in this study (66.00, IQR 21–85) and lower than for those not chronically infected or unaware of their infection. Taken together, this reinforces the view that HCV diagnosis can negatively affect QoL for PWID. Given that, the lack of change from baseline to follow-up was somewhat unexpected, as

previous research has shown positive improvements in QoL indicators both for non-PWID, and for PWID in receipt of OAT following HCV treatment with DAAs.<sup>39–42</sup> Our findings, taken together with the wider evidence, suggest further work is required to uncover mechanisms beyond therapeutic resolution of HCV to improve health-related QoL for PWID infected with HCV. Such research might investigate interventions which can be co-delivered alongside HCV therapy or concomitant to OAT collection. It may also suggest that other questionnaires should have been considered alongside the EQ-5D to ensure QoL was robustly measured from multiple angles, but this might have been onerous on participants.

This study has several strengths. The international nature suggests that the new model of care is feasible in diverse health systems. It lowered barriers to accessing HCV testing and treatment by co-locating these in venues routinely used by those at risk of infection. The sites involved were geographically and socio-economically diverse, suggesting the model is viable in pharmacies ranging from small to large, and in areas ranging from the least to the most socio-economically resourced. The main weakness of the study is that it did not obtain the pre-planned sample size of HCV-positive participants,<sup>18</sup> primarily due to the lower-than-expected level of HCV infection, but also due to previously mentioned restrictions placed on study activity consequent to the C-19 pandemic which limited engagement. In Tayside, where Scottish sites were located, recent evidence has shown a decrease in the prevalence of chronic HCV among PWID following rapid treatment scaleup,<sup>43</sup> while in Australia chronic HCV prevalence has also decreased following unrestricted access to DAAs.<sup>44</sup> In Wales, HCV infection rates per 100,000 have been trending downwards from 2019 to 21 (from 18.1 to 11.0).<sup>45</sup> The prevalence estimates which informed the study design predate these initiatives, and it may be that once the trial was started, prevalence had declined substantially leading to a lower-than-anticipated proportion of HCV-positive participants. Relatedly, C-19 placed substantial strain on conventional healthcare delivery, particularly in the United Kingdom, and moreover in community pharmacies, for the duration of the study, and that strain may have translated to decreased efficiency of the service relative to pre-pandemic. As a result of a smaller than planned sample size of HCV-positive participants, it was not feasible to perform

**FIGURE 3** Proportions of participants at critical steps of hepatitis c virus care cascade. RNA, ribonucleic acid; SVR12, sustained virologic response at 12 weeks. Proportions are sequential from previous steps. Raw data in Table S5



statistical comparisons in the mITT population. However, these comparisons were designed to explore associations at key steps of HCV care and were therefore not critical to determining the overall efficacy of the intervention pathway. Finally, study nursing staff could not be on-site every day, which limited engagement. Future studies may consider daily nursing presence in similar contexts, or a telemedicine approach to client engagement if feasible.

Overall, the intervention pathway is a safe and effective model of care which can improve engagement of OAT clients in HCV testing and treatment. The low levels of co-morbidity and liver disease suggest that minimal on-treatment monitoring is required, and non-specialist prescribers could be used to undertake pretreatment assessment for the majority of clients attending pharmacies for OAT. The model appears particularly suited to smaller pharmacies, so it

offers a viable alternative to other successful models which upskilled pharmacists and pharmacy support staff to deliver improved HCV care to OAT clients.<sup>13</sup> The intervention pathway could be a useful approach for those targeting HCV elimination and seeking an efficient means of engaging at-risk individuals in the community setting.

#### ACKNOWLEDGEMENTS

The research team acknowledge the contributions of all community pharmacists who participated, as well as the contributions of Eilidh Fergus (NHS Tayside), Linda Johnston (University of Dundee), Shirley Cleary (University of Dundee), Nicki Palmer (Public Health Wales), Kerry Rockey (Public Health Wales), Kate Allardice (Burnet Institute) and Kico Chan (Burnet Institute), for their key role in the successful delivery of the study under challenging circumstances.

**Declaration of personal interests:** CJB, SKI, NP, MDP, KA, HW and ER have nothing to disclose. AR reports he has received research grants from Gilead, Bristol Myers Squibb, Abbvie and Roche and has received honorariums from Gilead and personal fees from Abbvie. LB reports grants from NIHR during the conduct of the study. DS and MH are employees of AbbVie and may hold stock in AbbVie. BH reports personal fees and other from Abbvie, personal fees and other from Gilead, outside the submitted work. JSD reports grants and personal fees from AbbVie, grants and personal fees from Gilead Sciences, and grants Bristol Myers Squibb, outside the submitted work. JFD reports grants and personal fees from Abbvie; grants and personal fees from Gilead, grants and personal fees from MSD outside the submitted work.

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## SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

**How to cite this article:** Byrne CJ, Radley A, Inglis SK, Beer L, Palmer N, Duc Pham M, et al. Reaching people receiving opioid agonist therapy at community pharmacies with hepatitis C virus: an international randomised controlled trial. *Aliment Pharmacol Ther*. 2022;55:1512–1523. <https://doi.org/10.1111/apt.16953>