

BMJ Open Randomised controlled trial conducted in injecting equipment provision sites to compare the effectiveness of different hepatitis C treatment regimens in people who inject drugs: A Direct observed therapy versus fortNightly Collection study for HCV treatment—ADVANCE HCV protocol study

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To cite: Inglis SK, Beer LJZ, Byrne C, *et al.* Randomised controlled trial conducted in injecting equipment provision sites to compare the effectiveness of different hepatitis C treatment regimens in people who inject drugs: A Direct observed therapy versus fortNightly Collection study for HCV treatment—ADVANCE HCV protocol study. *BMJ Open* 2019;**9**:e029516. doi:10.1136/bmjopen-2019-029516

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2019-029516>).

Received 29 January 2019
Revised 17 June 2019
Accepted 02 July 2019



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ABSTRACT

Introduction Hepatitis C is a blood-borne virus (HCV) that can seriously damage the liver and is spread mainly through blood-to-blood contact with an infected person. Over 85% of individuals who have HCV in Scotland became infected following injecting drug use. Since people who inject drugs (PWID) are the main source of new infections, theoretical modelling has suggested that treatment of HCV infection in PWID may effectively reduce HCV prevalence and accomplish elimination. This protocol describes a clinical trial delivering HCV treatment within injecting equipment provision sites (IEPS) in Tayside, Scotland.

Methods and analysis PWID attending IEPS are tested for HCV and, if they are chronically infected with HCV and eligible, invited to receive treatment within the IEPS. They are randomised to one of three treatment regimens; daily observed treatment, treatment dispensed every 2 weeks and treatment dispensed every 2 weeks together with an adherence psychological intervention (administered before treatment begins). The primary outcome is comparison of the rate of successful treatment (SVR₁₂) in each treatment group. Secondary analyses include assessment of adherence, reinfection rates, viral resistance to treatment and interaction of the treatment with illicit drugs.

Ethics and dissemination The ADVANCE (A Direct observed therapy versus fortNightly Collection) HCV trial was given favourable opinion by East of Scotland Research Ethics Committee (LR/17/ES/0089) prior to commencement.

Trial registration numbers European Clinical Trials Database (EudraCT) (2017-001039-38) and ClinicalTrials.gov (NCT03236506).

Strengths and limitations of this study

- Pragmatic trial based in injecting equipment provision sites (IEPS) and designed to fit around the needs of people who inject drugs.
- Aims to deliver hepatitis C virus diagnosis, evaluation and treatment in one site based within the community.
- Strengthens links with local third-sector organisations promoting sharing of knowledge which clinicians are unlikely to be otherwise able to access.
- Trial is being conducted in a single health board; National Health Service Tayside in Scotland, UK.
- Participants are incentivised to attend treatment by way of nutrient drinks and payment of return bus fare to the IEPS which may not be available beyond the clinical trial setting.

INTRODUCTION

Hepatitis C virus (HCV) is a blood-borne virus that can seriously damage the liver and is spread mainly through blood-to-blood contact with an infected person. Globally, an estimated 71 million people have chronic HCV infection and the WHO has targeted elimination of HCV as a public health threat by 2030, through reducing new infections by 90% and reducing viral hepatitis-related deaths by 65%.¹ The ‘serious and significant public health risk’ posed by HCV was recognised during a member’s debate in the Scottish Parliament in 2004.² By December 2006, Health Protection Scotland estimated

that 50 000 persons in Scotland had been infected with HCV and that 38 000 were chronically infected.^{3 4} Estimates in 2017 placed current prevalence in Scotland at 1% of the population, which increases to 58% among those people who inject drugs.^{5 6} Thus, it is clear that the greatest risk of acquiring the virus in the UK is through injecting drug use. In Scotland, it is estimated that over 85% of individuals who have HCV were infected in this way.⁷

The outcome of HCV infection varies considerably between individuals. Up to 25% are able to clear the infection spontaneously, while the remaining 75% become chronically infected.⁸ Of those chronically infected, 10%–20% will develop serious liver disease, including cirrhosis and hepatocellular carcinoma, within 30 years.^{9 10} Many who are infected are unaware of it, and often show no symptoms over a long period of time. While there is presently no vaccination for HCV, the recent introduction of directly acting antiviral treatments (DAA) has begun a new era in treatment of this disease.¹¹ These new oral treatments are safe, have shorter treatment regimens than previous medications and are effective, producing a cure in over 95% of cases providing adherence is adequate.¹²

The advent of very effective DAA therapies enables the use of treatment as prevention (TaSP), by targeting treatment to people who inject drugs (PWID) who are the main source of new infections and reinfections. Implementation of TaSP strategies to HIV, including scaling up treatment and increasing rates of testing, has successfully reduced incidence and rate of new HIV infections.^{13 14} Indeed, modelling work illustrates that HCV treatment is a critical component of HCV prevention among PWID and is likely to be cost-effective compared with delaying treatment or treating non-PWID with mild or moderate disease.^{15–19} For example, Martin *et al* show that in a population where chronic HCV prevalence in PWID is below 60% and 10–20 per 1000 PWID are treated per year, HCV prevalence can be reduced by 10%–80% over 20 years depending on the modelling of successful treatment rates and retreatment of treatment failures.¹⁵ The scale of the benefit is inversely and exponentially related to prevalence of HCV in the population; the lower the prevalence the sooner and larger the impact.¹⁵

Conventional treatment pathways focus on treating people who no longer inject drugs and tend to engage in fewer high-risk behaviours compared with PWID. Treating this group will reduce future morbidity in the individuals themselves but is unlikely to achieve additional benefit in terms of averting future infections, whereas providing HCV testing and treatment to PWID is also likely to reduce the spread of new infections. Treating this population has proved challenging since there are myriad barriers that deter PWID from seeking treatment.^{20 21} These include stigma that leads to discrimination against PWID in health settings.²² Patients themselves may perceive their risk of infection to be low; they may currently be symptomless and may fear the treatment.²³ In addition, the

belief that PWID will demonstrate poor adherence to treatment and may have poor rates of successful treatment due to illicit drug or alcohol use has hindered treatment opportunities.²²

Over the past 6 years, treatment and care for people with HCV living in National Health Service (NHS) Tayside has been comprehensively scaled up, and numerous novel treatment pathways have been established. Together with a conventional hospital-based hepatitis treatment service, treatment has also been embedded within the community via a combination of NHS and clinical trial-based delivery in sites including: addiction treatment centres/community clinics, community pharmacies,²⁴ prisons and injecting equipment provision sites (IEPS).²⁵ Testing and treatment is led by specialist nurses with clinician oversight as required. DAA regimens that have negligible side effects are now the standard of care in conventional treatment populations. DAAs should be taken daily to optimise therapeutic success and therefore if adherence is poor, efficacy might be reduced. The rate of successful treatments combined with medication cost, reinfection rate and emergence of viral resistance will determine if this treatment as prevention model is cost-effective with DAAs.

This paper describes the ADVANCE (A Direct obserVed therApy versus fortNightly CollECTION) HCV study protocol (V5, 02/04/2018), a clinical trial of investigational medical product delivering DAA treatment for HCV to PWID in IEPS in NHS Tayside. These sites provide sterile injecting equipment and basic healthcare for PWID including testing and treatment for blood-borne viruses by specialist nurses. Signposting to other services is also provided, while opioid replacement therapy is not provided. The aim of the study is to demonstrate that PWID can successfully be treated for HCV using DAA treatment. The effectiveness of three different medication dispensing regimens is being determined by measuring the rates of sustained viral response at 12 weeks (SVR₁₂), considered a successful treatment, of individuals treated via each regimen. The first regimen is directly observed therapy (DOT), the second regimen is to provide medication on a fortnightly basis, while the third regimen is to provide medication on a fortnightly basis together with a 1-hour psychological intervention designed to improve adherence, delivered before treatment commences. While DOT is often considered the ultimate adherence aid, it has not previously been trialled in this patient group, although it has been successfully used to treat PWID for HIV infection.²⁶ We hypothesise that the fortnightly (with or without adherence) treatment regimens will not be inferior to DOT and will result in similar rates of SVR₁₂.

This trial is part of a wider suite of trials and studies which will analyse the cost-effectiveness of the TasP approach to HCV treatment. The study is underway, with the first recruit in January 2018, and recruitment is predicted to end in December 2019. Data collection will be completed in September 2020.

METHODS AND ANALYSIS

Objectives and outcome measures

Primary objective

To compare the efficacy of DAAs in HCV positive, active PWID, administered via DOT, fortnightly pick-up or fortnightly pick-up with a psychological adherence intervention.

Outcome measure

SVR₁₂ rates of participants in the DOT, fortnightly pick-up or fortnightly pick-up with a psychological adherence intervention group.

Time point of outcome measured

Twelve weeks post-treatment completion.

STUDY DESIGN

Study set up

Sponsorship is provided via a joint agreement between NHS Tayside and the University of Dundee. A clinical trial authorisation was provided by the Medicines and Healthcare Products Regulatory Agency in September 2017. Overall management of the trial is being provided by the Tayside Clinical Trials Unit, a UK Clinical Research Collaboration-registered clinical trials unit.²⁷ The trial is being monitored by the sponsor according to an agreed monitoring plan in accordance with the sponsor standard operating procedures. Specialist nurses experienced at providing HCV treatment within the IEPS were trained in good clinical practice and were given study-specific training. The first participant was recruited in January 2018.

Design

The study is a parallel three-arm randomised trial comparing the efficacy of DAAs for treatment of HCV in PWID. The three arms are: (1) DAA dispensed via directly observed therapy; (2) DAA dispensed fortnightly and (3) DAA dispensed fortnightly following a single-session psychological intervention on treatment adherence.

HCV treatment

Participants are treated with Zepatier (a single 150 mg tablet comprising 100 mg grazoprevir and 50 mg of elbasvir) provided gratis by Merck Sharpe & Dohme. Individuals infected with HCV genotype 1 are treated with 1 tablet per day for 12 weeks, as per the marketing authorisation for this medication. Individuals infected with genotype 3 are treated with 1 tablet of Zepatier, plus 1 tablet of Sovaldi (Sofosbuvir 400 mg) purchased via NHS Tayside (the local health board) per day for 8 weeks. This is an unlicensed treatment combination but has been used successfully to treat individuals with genotype 3 infection in previous trials.²⁸

Eligibility criteria

The inclusion criteria are deliberately broad and the exclusion criteria minimal. This is to ensure that the study captures a typical group of PWID using IEPS and

requiring anti-HCV treatment and is therefore relevant to populations in other similar clinics. Almost all infections within NHS Tayside result from genotype 1 and 3 HCV.³ Participants who have been treated for HCV with DAAs previously are referred to the NHS Tayside multi-disciplinary team (which includes hepatologists, specialist doctors, HCV pharmacists and specialist nurses) for review and determination of appropriateness for treatment through the trial.

Inclusion criteria:

- ▶ Aged 18–70.
- ▶ HCV PCR confirmed active infection, genotype 1 or 3.
- ▶ If female, must have negative urine test results for pregnancy during initial screening period (for trial inclusion) and be advised of limited safety data in pregnancy.
- ▶ Current illicit drug use established through participant history.
- ▶ Able to provide informed consent, agreeing to trial and clinical monitoring criteria.

Exclusion criteria:

- ▶ Aggressive or violent behaviour.
- ▶ Unwilling to consent to general practitioner being informed of their participation in the trial.
- ▶ Pregnancy or breast feeding.
- ▶ Participation in a drug trial within the previous 30 days.
- ▶ Platelet count $<75 \times 10^9/L$.
- ▶ Alanine transaminase $>350 U/L$.
- ▶ Clinical history or blood test results consistent with decompensated liver failure Childs-Pugh B or C.
- ▶ Clinical history of primary hepatocellular carcinoma.
- ▶ Hepatitis B surface antigen positive.
- ▶ HIV infection.
- ▶ Hypersensitivity to elbasvir and grazoprevir.
- ▶ Hypersensitivity to sofosbuvir (genotype 3-infected participants only).
- ▶ Currently being treated with an inhibitor of organic anion transporting polypeptide 1B, for example, rifampicin, atazanavir, darunavir, lopinavir, saquinavir, tipranavir, cobicistat or ciclosporin.
- ▶ Currently being treated with inducers of cytochrome P450 3A or P-glycoprotein, such as efavirenz, phenytoin, carbamazepine, bosentan, etravirine, modafinil or St John's Wort (*Hypericum perforatum*).
- ▶ Currently being treated with amiodarone (participants infected with genotype 3 HCV only).

Enrolment

Individuals attending IEPS are routinely invited to have a dry blood spot test (DBST) for HCV. Individuals who have had a positive DBST or have previously had a positive PCR blood test result for HCV are identified by trained nurses working in the IEPS and provided with verbal and written information about the trial in the form of a patient information sheet. The levels of literacy of some individuals in this group are likely to be low, and this was taken into account during the preparation of all patient-facing

written material. At least 24 hours after being given information about the trial, individuals who return to the IEPS are asked whether they would like to take part. Sometimes individuals will not return to the IEPS for many days or even weeks after receiving information about the trial. In these cases, they are reminded about the trial and then asked whether they would like to take part. If the participant is willing, informed consent is obtained by the nurse. Ongoing informed consent is checked and documented at each study visit.

Randomisation

Participants are randomly assigned to treatment regimens using the Tayside Randomisation System (TRuST). TRuST is a web-based randomisation system developed and maintained by Health Informatics Centre at University of Dundee. Participants are stratified according to their gender and HCV genotype.

Visit schedule

All study visits take place within the IEPS which is a familiar environment to the people eligible for the trial. Visits are conducted by specialist nurses and, in accordance with good clinical practice, trained, delegated clinicians sign-off blood test results and eligibility checks. Individuals infected with HCV genotype 3 have 8 weeks of treatment and attend 4 study visits (table 1). Those infected with genotype 1 have 12 weeks of treatment and attend 5 study visits (table 1). The extra study visit includes blood taken for liver function testing to detect any elevated alanine aminotransferase (ALT) levels (>350 U/L) that are an occasional side effect of Zepatier taken for longer than 8 weeks.²⁹ Any participant with an ALT level >350 U/L will have their treatment stopped and will be followed up to SVR₁₂.

Since individuals frequently have periods during which they do not attend the IEPS, the time periods during which visits can take place have deliberately been left as long as possible. Occasionally, participants are incarcerated during their period on treatment. In this case, treatment is transferred to the prison pharmacy and the participant's treatment is maintained by the nurses working there with all participants receiving daily treatment. These nurses are part of the clinical hepatitis team and operate an established Blood borne virus treatment pathway through prisons in the region, headed by the study chief investigator which ensures a continuity of care. If an individual misses more than seven consecutive doses they will be withdrawn from treatment but still followed up to the SVR₁₂ visit.

At the baseline visit, blood samples are taken for safety tests (including urea and electrolytes, liver function tests, full blood count, prothrombin time and pregnancy testing for women) and diagnostic tests (HCV PCR and genotyping). Baseline demographic information together with information about illicit drug habit and social history are recorded in the case report form (CRF). To retain as many eligible individuals in the study as possible, the blood test

results and information in the CRF are considered valid for 6 months. Therefore, as long as the randomisation visit is completed within 6 months of the baseline visit, the baseline visit does not need to be repeated. Due to time constraints on testing imposed by NHS Tayside laboratories HCV PCR results are valid for 1 year and genotype results valid for 5 years.

Patients are randomised to one of the three treatment regimens and stratified by sex and genotype of the HCV infection.

At the randomisation visit, the participant is told to which study arm they have been allocated. A description of the three arms is provided below.

At the end of treatment visit, blood samples are taken for safety reasons, and information about illicit drug use and social situation collected to detect any change concomitant with treatment.

At least 12 weeks following the end of treatment, blood is taken for the HCV PCR test to measure whether viral RNA can be detected.

Blood samples are taken at baseline, end of treatment and SVR₁₂ and stored at -80°C . Samples collected from individuals who do not achieve SVR₁₂ will be analysed at the end of the study for the presence of HCV RNA that has mutated to become resistant to DAA.³⁰ A urine sample is also collected from individuals at any time while they are on treatment and stored at -80°C . These samples may be analysed at the end of the study to detect the presence of illicit drugs/metabolites that may interact and reduce the effectiveness of DAA treatment only for those that do not achieve SVR₁₂ despite good adherence to treatment. Both blood and urine samples are anonymised and stored without personal identifying information. The key that removes the anonymisation is held securely, separately from the samples, within the clinical team.

DOT treatment regimen

Those in the DOT arm are asked to attend every weekday when they are given their tablet and observed taking it. Doses for the weekend (and any holidays when the IEPS is closed) are given to the participant to take away. Travel expenses, in the form of local service, return trip bus fare and nutrient drinks are given to encourage daily attendance.

Fortnightly treatment regimen

Those randomised to either of the fortnightly dispense arms are given a 2-week supply of medication with instructions to take one dose per day. Participants are asked to return any packaging together with untaken medication to each study visit. Participants who have genotype 3 HCV receive Sovaldi tablets in bottles that are fitted with a Medical Event Monitoring (MEM) cap (Westrock Switzerland, MEMS8 TrackCap 38mm CR). Participants are asked to return the caps at the end of treatment, and they are scanned to assess participant adherence. Travel expenses, for study visits and drug collection days, in the form of local service, return trip bus fare and nutrient drinks are given to encourage daily attendance.

Table 1 Schedule of visits

Study visits	Baseline	Randomi-sation	Visit 3	Visit 4	End of treatment	SVR ₁₂
Timeline (participants infected with genotype 1 HCV)		Day 0	Week 4 (-7 to +14 days)	Week 8 (-7 to +14 days)	Week 12 (-7 to +14 days)	Week 24 (+12 weeks)
Timeline (participants infected with genotype 3 HCV)		Day 0	Week 4 (-7 to +14 days)	N/A	Week 8 (-7 to +14 days)	Week 20 (+12 weeks)
Informed consent	X					
Check inclusion/exclusion criteria	X					
Medical history	X					
Drug misuse history	X				X	
Urine test for illicit drugs		*	*	*	*	
Demographics	X					
Blood tests; Urea and electrolytes, Full blood count, Prothrombin time	X				X	
Blood tests; Liver function tests	X			X	X	
Blood test; PCR	X				X	X
Research blood	X				X	X
Urine pregnancy test	X					
Adverse event assessment		X	X	X	X	X
Record or review con meds	X	X	X	X	X	X
Check medication compliance			X	X	X	
Antiviral medication administration		X	X	X	X	
Psychological interview for those randomised to this intervention	X					

Continued

Table 1 Continued

Study visits	Baseline	Randomi-sation	Visit 3	Visit 4	End of treatment	SVR ₁₂
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*Urine sample collected once during treatment.
SVR, sustained viral response.

Fortnightly treatment regimen with psychological intervention

Participants randomised to receive the psychological intervention designed to promote adherence receive it at the randomisation visit before they take their first dose. The intervention, which lasts around 1 hour, is based on the Information-Motivation-Behavioural (IMB) Skills Model of Adherence³¹ which was originally developed to explain adherence behaviour in HIV. Recent research suggests this model may have applicability in understanding the facilitator and barriers to adherence in patients with HCV.³² The model suggests that provision of medication information, enhancing personal and social motivation and developing behavioural skills linked to determinants of adherence may improve adherence in this group. As part of the intervention, participants complete a personalised booklet, 'Hepatitis C and Me', with the guidance of their trial nurse. The booklet contains general and personalised information on HCV, exercises designed to explore and enhance personal and social motivation for treatment adherence and a behavioural action plan (the skills element of the IMB model). The booklet uses the principles of node-link mapping to structure the intervention, using the visual representation of interrelationships between thoughts, actions, feelings, triggers of personal problems and their hypothetical solutions.³³ Participants in the other two arms of the trial, who are not receiving the psychological intervention, are given the current NHS Tayside hepatitis information which provides generalised information about HCV without personalised information or specific strategies to enhance motivation and behavioural skills. Treatment is dispensed as described in Fortnightly treatment regimen above.

Sample size calculation

We hypothesise that DAA treatment in active PWID administered fortnightly with or without adherence intervention is non-inferior to DOT. Pathways will be compared sequentially; DOT versus fortnightly delivery and then DOT versus fortnightly pickup with adherence intervention. Fortnightly pick up will be more cost-effective than the other two options so long as adherence and efficacy matches that of the DOT and fortnightly plus adherence intervention. If we assume a 95% SVR₁₂ rate (based on published studies, eg, reference³⁴⁻³⁶) in the DOT arm of the trial in this population and a non-inferiority limit of 14% which would be likely to maintain clinical effectiveness, then at a 5% significance level and 90% power, we require a sample size of 42 in each group, making 126 in total. To allow for dropouts, we will aim to randomise 135 individuals; 45 per group.

Data collection and management

To ensure that participants are not subjected to long study visits the number of datapoints collected in the trial has deliberately been kept small and limited to fields required to answer objectives. Data collected at each study visit is entered into a paper CRF. The data are subsequently entered into an electronic version of the CRF developed

within Openclinica open source software V.3.1.3.1.³⁷ Data are stored in an anonymised state, identified by trial number. No personal information is shared with individuals outwith the local clinical care and research team. A key that links trial number to personal identifiers that could be used for record linkage is held separately and securely on NHS servers.

Safety reporting

Previous experience of recruiting PWID to clinical trials has revealed that many have comorbid chronic disease and high levels of illness.²⁵ In addition, injuries from accident and assault are also common. To ensure that safety reporting is restricted to events related to the trial, we record as adverse events (AE)s/serious adverse events (SAE)s but not report as SAEs in the following categories:

- ▶ Any death or hospitalisation for assault or accidental injury.
- ▶ Hospitalisation for abscesses due to drugs use.
- ▶ Hospitalisation for wound management due to drugs use.
- ▶ Any death or hospitalisation due to non-HCV infection.
- ▶ Hospitalisation for elective or planned investigation or treatment.
- ▶ Any death or hospitalisation for deteriorating renal function, high or low potassium levels.
- ▶ Any hospitalisation due to nausea, vomiting, constipation or diarrhoea.

Analysis plan

The primary outcome of SVR₁₂ will be assessed as a binary outcome for subjects and so will use logistic regression modelling. The numerator will be the number of subjects achieving SVR₁₂, and the denominator will be total number of patients randomised to each arm. Additionally, results will be expressed as a proportion of the estimated HCV-infected subjects using the IEPS. The estimated number of infected patients will be based on national survey data and the empirical rate discovered in the trial (allowing for patients who refuse testing). A test of interaction between contingency and pathway will be carried out and, if not significant, contingency will be assessed independently. If significant, then the effect of contingency will be assessed by each pathway separately. As all patients will have either achieved SVR₁₂ or not, and we will assume that dropouts/lost to follow-up are failures, there will be no missing data in the primary outcome. Extrabinomial variability or overdispersion will be examined in the logistic model and if present alternative modelling such as negative binomial models will be considered. This will also be adjusted by treatment and genotype; the two factors are interdependent determining length of regimen.

Secondary binary outcomes will be analysed in the same procedure, initially as intention to treat with all eligible patients as the denominator and then to explore the steps

in the pathway by per protocol analysis in particular to analyse:

- a. Proportion of HCV tested who are HCV positive.
- b. Proportion of those identified with HCV who start HCV treatment within the duration of the study.
- c. Adherence in each treatment regimen.
- d. Proportion of those initiating treatment who complete the treatment course.
- e. Reinfection rates (of trial cohort HCV status via national laboratory testing data for up to 5 years).

Multiple logistic regression modelling will explore the patient and pathway characteristics that are associated with the secondary outcomes and primary outcome. Patient outcomes considered will be age, gender, deprivation, employment, comorbidity and the psychosocial variables assessed.

Patient and public involvement statement

Patient and public were not involved in the design of this study. However, in cognate ongoing studies we are conducting interviews with participants to collate their experience of the provided through this study.

ETHICS AND DISSEMINATION

The study results will be disseminated through peer-reviewed publications, presented at conferences and published on clinicaltrials.gov and Eudract websites. The anonymised dataset will be held by the chief investigator. Consideration will be given to applications from other researchers who apply for access to the data for their own research.

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Acknowledgements The study team acknowledge people who inject drugs within Tayside who are participating in the study. In addition health professionals including pharmacists, prison workers and the wider clinical team working within NHS Tayside. The team also acknowledge MSD who are funding the study.

Contributors SI contributed to study design, wrote the trial protocol, provided study-specific training to study team, managed the study and wrote the manuscript. LB ran the study, provided study-specific training to study team and revised the manuscript. CB revised the manuscript and provided study-specific training to study team. AM provided the psychological intervention booklet training to study team and revised the manuscript. JFD is chief investigator. KG designed the psychological intervention and approved the manuscript. EMR delegated clinician on the study and revised the manuscript. CS is a specialist nurse who undertook study visits. BS is the lead specialist nurse.

Funding This study was funded by Merck Sharp and Dohme (grant number:53605).

Competing interests SI, CB, AM, LB, ER, CS and KG have no competing interests. BS has received honoraria for lectures from Abbvie, Janssen, Gilead, and MSD. JFD has received personal honoraria for lectures and institutional research grants from MSD, Abbvie, Gilead, Roche and Janssen.

Ethics approval Ethical approval was obtained from the East of Scotland Research Ethics Service (17/ES/0089; August 2017). The study is being conducted according

to the principles of the Declaration of Helsinki and in accordance with the Research Governance Framework Scotland.

Provenance and peer review Not commissioned; externally peer reviewed.

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