PEER REVIEW HISTORY

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Clinical effectiveness of pharmacy-led versus conventionally delivered antiviral treatment for Hepatitis C in patients receiving opioid substitution therapy: A study protocol for a pragmatic cluster randomised trial
AUTHORS	Radley, Andrew; De Bruin, M; Inglis, Sarah Karen; Donnan, Peter; Dillon, John F

VERSION 1 – REVIEW

REVIEWER	Angelos Hatzakis National and Kapodistrian University of Athens Medical School Greece
REVIEW RETURNED	14-Feb-2018

GENERAL COMMENTS	This is a well designed study. However, I have some concerns: 1. A limitation I can see is the risk of violating randomization (e.g. PWIDs in the same city frequently know personally each other. Participation in a pharmacist-led pathway might be preferable and PWIDs may change pharmacy resulting in selection bias). 2. PWIDs with compensated cirhossis might prefer the conventional care pathway resulting again the selection bias. 3. Safety issues are expected to be uncommon. However, a more formal assessment of potential side effects or other safety issues is recommended.

REVIEWER	Maryam Alavi Kirby Institute, UNSW Sydney Australia
REVIEW RETURNED	23-Mar-2018

GENERAL COMMENTS	The protocol entitled "SuperDOT-C: Clinical effectiveness of pharmacy-led versus conventionally delivered antiviral treatment for Hepatitis C in patients receiving opioid substitution therapy: a pragmatic cluster randomised trial" describes a cluster randomised trial to evaluate the impact of pharmacy-delivered hepatitis C treatment on antiviral treatment success rates amongst people receiving opioid substitution therapy in Scotland. The protocol is well-written and rationale and details relating to methods are described clearly. This community pharmacist-led hepatitis C

	treatment model is designed based on several aspects of delivering hepatitis C care to difficult to reach populations, including interlinking infrastructure and providing a simplified cascade of hepatitis C care. Findings from this study could significantly contribute to the field.

REVIEWER	April Young University of Kentucky, USA
REVIEW RETURNED	29-Mar-2018

GENERAL COMMENTS	Overall, the manuscript is well written and the protocol is innovative and described clearly. Relatively minor revisions would strengthen the manuscript. The manuscript would benefit from a more clear description of the study's limitations and the timeline for enrollment and follow-up (i.e., if the trial is 18 months long, it is unclear how many participants will be able to contribute to the re-infection outcome analysis given that re-infection is being assessed at 12 months). The authors should also add a brief explanation of methods that they are using (if any) for participant retention. It would be helpful for readers to have a more explicit description of the standard OST regimen and how frequently patients interact with pharmacists for OST. It is unclear whether all patients in the trial are on the same OST regimen and to what degree they have to compliant with OST to be eligible for the trial (and how "compliance" is defined). The numbers in the power calculation are somewhat unclear. The authors report that there is an average of 30 subjects per pharmacy (Line 52, Page 11) and report that the average infected subjects per pharmacy is 20 (Line 49, Page 11); this is a 66% prevalence rate, but the authors cite national data that only 40% of patients on OST are HCV positive (Line 37, Page 11). The authors should make it more clear how they arrived at their power calculation. Finally, the authors should check abbreviations used throughout the manuscript and make sure that they are defined at first use.

VERSION 1 – AUTHOR RESPONSE

Reviewers Comments	**Study Team Response.**
Reviewer 1 - Angelos Hatzakis This is a well designed study. However, I have some concerns:	The study team thank the reviewer for his comments.
R1.1 A limitation I can see is the risk of violating randomization (e.g. PWIDs in the same city frequently know personally each other. Participation in a pharmacist-led pathway might be preferable and PWIDs may change pharmacy resulting in selection bias).	Within Dundee, almost all prescriptions for Opioid Substitution Therapy (OST) are written by the Specialist Substance Misuse Team. PWIDs receiving a prescription are placed with a pharmacy. The numbers of free spaces within pharmacies providing supervision of OST at any one time is restricted. Thus the potential for significant numbers of PWIDs changing pharmacies in order to specifically access the pharmacy-led pathway is very small. A further

Reviewers Comments	Study Team Response.
	factor that will minimise this effect is that it is normal practice in Tayside for treatment to be delivered within the participant's local pharmacy. Thus after assessment and commencement on therapy within the standard of care pathway, the individual would be returned for completion of their course at their normal pharmacy.
R1.2 PWIDs with compensated cirrhosis might prefer the conventional care pathway resulting again the selection bias	We have added the following text inserted into the manuscript: 'Within the protocol, potential participants with a FIB-4 score of > 3.25 are referred on to the Standard of Care Pathway for review. The Pharmacist-led Pathway therefore excludes this group from being entered into the trial. Instead, they are assessed for treatment through the Standard of Care Pathway where they are reviewed in hospital by a medical consultant who decides if it is safe to proceed with treatment and if yes, may select different drugs. Note also that this does not result in selection bias given that the whole population of OST users in the participating pharmacies are included in the denominator.
R1.3 Safety issues are expected to be uncommon. However, a more formal assessment of potential side effects or other safety issues is recommended.	Yes agreed. We have been too succinct in our descriptions and have now clarified that we are monitoring adverse events on a daily basis, i.e. every time that patients pick up their medication from the pharmacy a daily log is completed, recording any occurrence of side-effects or adverse events. Additional text inserted into the manuscript
Reviewer 2 - Maryam Alavi The protocol entitled "SuperDOT-C: Clinical effectiveness of pharmacy-led versus conventionally delivered antiviral treatment for Hepatitis C in patients receiving opioid substitution therapy: a pragmatic cluster randomised trial" describes a cluster randomised trial to evaluate the impact of pharmacy-delivered hepatitis C treatment on antiviral treatment success rates amongst people receiving opioid substitution therapy in Scotland. The protocol is well-written and rationale and details relating to methods are described clearly. This community pharmacist-led hepatitis C treatment model is designed based on several aspects of delivering hepatitis C care to difficult to reach populations, including interlinking infrastructure and providing a simplified cascade of hepatitis C care. Findings from this study could significantly contribute to the field.	The study team thank the reviewer for her comments.

Reviewers Comments	Study Team Response.
Reviewer 3 - April Young Overall, the manuscript is well written and the protocol is innovative and described clearly. Relatively minor revisions would strengthen the manuscript.	The study team thank the reviewer for her comments
R3.1 The manuscript would benefit from a more clear description of the study's limitations and the timeline for enrolment and follow-up (i.e., if the trial is 18 months long, it is unclear how many participants will be able to contribute to the re-infection outcome analysis given that re-infection is being assessed at 12 months).	Additional text inserted into the manuscript. People prescribed Opioid Substitution Therapy (OST) are retained in the service for many years, since their progress of recovery and becoming drug-free is slow. In addition, movement out of Dundee, which is relatively geographically isolated, is minimal. We are therefore confident that we can identify all patients still in receipt of a prescription for OST and invite them to be re-tested for Hepatitis C. Since the network of pharmacies providing OST, are also trained to provide testing, we believe this is feasible. Annual testing of at-risk PWIDS is already implemented as part of local health policy.
R3.2 The authors should also add a brief explanation of methods that they are using (if any) for participant retention.	Additional text inserted into the manuscript: 'Participants are likely to be retained within the study through the mechanism of daily attendance for receipt of supervised OST; this is a powerful mechanism making people return to the pharmacy. It is intended that data will still be collected on participants who may not complete their course of treatment, since partial completion may produce an SVR also. Note that retention is only relevant for those who start treatment, given that those who do not test or start treatment are assumed to not achieve SVR.
R3.3 It would be helpful for readers to have a more explicit description of the standard OST regimen and how frequently patients interact with pharmacists for OST. It is unclear whether all patients in the trial are on the same OST regimen and to what degree they have to compliant with OST to be eligible for the trial (and how "compliance" is defined).	The reviewer is correct in that participants are not all on the same regimen for their OST – some daily others weekly. However, to be eligible for the study they had to agree to daily OST therapy for the length of their treatment course Additional text inserted into the manuscript: 'Patients who are referred for assessment and treatment will be managed according to the standard local treatment pathway. Daily supervised OST treatment is delivered by the pharmacy, in which the doses of methadone or buprenorphine are provided by the pharmacy staff, who observe consumption. In both arms of the study DAA treatment is delivered jointly with OST in their normal pharmacy; which would qualify as DOT during weekdays, although at weekends patients usually self-administer.'

Reviewers Comments	Study Team Response.
R3.4 The numbers in the power calculation are somewhat unclear. The authors report that there is an average of 30 subjects per pharmacy (Line 52, Page 11) and report that the average infected subjects per pharmacy is 20 (Line 49, Page 11); this is a 66% prevalence rate, but the authors cite national data that only 40% of patients on OST are HCV positive (Line 37, Page 11). The authors should make it more clear how they arrived at their power calculation.	The line referred to (Line 49, Page 11) is included to show that the cluster design is capable of delivering a significant result if an inflationary effect in infection rate is used. The reviewer is quite correct in identifying that we expect only 40% of PWIDs receiving OST to be infected with HCV which would imply the number per pharmacy on OST with HCV would be 12. This has been corrected in the text.
Editorial Office Comment: The authors should check abbreviations used throughout the manuscript and make sure that they are defined at first use	The study team thank the Editorial Office for their helpful comments. This point is now addressed.

VERSION 2 – REVIEW

REVIEWER	Angelos Hatzakis National and Kapodistrian University of Athens Medical School,-Greece
REVIEW RETURNED	21-May-2018

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.

REVIEWER	April Young University of Kentucky, United States
REVIEW RETURNED	30-May-2018

GENERAL COMMENTS	The manuscript is much improved. My only remaining suggestion is that the authors revise the Introduction of the abstract so that it is clear that the prevalence estimates cited refer to prevalence in Scotland / the UK.