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)	The impact of drug consumption rooms on risk practices and access to care in people who inject drugs in France: the COSINUS prospective cohort study protocol.
AUTHORS	Auriacombe, Marc; Roux, Perrine; Briand Madrid, Laélia; Kirchherr, Sébastien; Kervran, Charlotte; Chauvin, Carole; Gutowski, Marie; Denis, Cécile; Carrieri, Maria Patrizia; Lalanne, Laurence; Jauffret-Roustide, Marie; COSINUS, Study Group

VERSION 1 – REVIEW

REVIEWER	Ali Mirzazadeh University of California San Francisco (UCSF), USA
REVIEW RETURNED	16-Jun-2018

GENERAL COMMENTS	I would like to thank authors for all their efforts to design and run this important Cohort in France and also drafting the manuscript to share the study methods. I really enjoyed reading the manuscript and have some suggestions and questions for the authors to improve it – they are listed below: **Introduction:** The introduction is heavily discussed the history of HIV and response which is not fully relevant but missed two main things to discuss - The consequences of public injecting and drug use - The current evidence about safety and efficacy of DCR on risk-behaviors, over-dose and HIV/HCV infections. **Research objectives and hypothesis:** - While in the abstract and the introduction, HIV and HCV have reports as main outcomes of the study, nothing has mentioned about the hypothesis on the association between DCR and the two infections? - One of the major benefits of DCR is to reduce the over-dose related mortality. This was not mentioned as study outcomes. If there is a plan to measure this effect, details need to be added. If there is no plan, justification need to be provided why it was not measured. **Study design:**

	- Rational for choosing the two cities for the DCR intervention and also particularly rational for choosing the two control cities need to be provided. **Participants:** - What does “regular user” means? Please provide clear definition for it? - How injection in last month will be verified? Is it only measured by self-report? - How likely two persons have same “month, year and place of birth” and so records of these two were mixed up? - Not clear of HIV-positive or HCV-negative will be eligible to participate in the cohort? - Is there any condition that make participants ineligible for study, i.e. what are the exclusion criteria? **Key exposure measurement** - It looks like the enrollment in the cohorts are DCR sites in the two cities that have DCR sites and from other harm reduction sites in the two cities that do not have DCR sites. - And then in the measurement section, DCR exposure was measured by questionnaire and self-report which is not a perfect way. I am wondering why it is not measured by linking the records at DCR to study participants by some links like date of birth etc. **Sample size:** - What does “regularly attend” means in the following statement: “different countries with DCR have shown that between 30%36 37 and 60%38 of users regularly attend them” - Based on what the sample size allocated to the four cities? **Statistical analysis:** - It was not clearly mentions how the “combined effect” of DCR together with other HR services will be assessed? How this combined effect will be developed and what model will be used to assess it? - It was not clear how the loss to follow up will be assessed and analyzed **Discussion:** - I am wondering if study has any limitation that need to be acknowledged like self-report measurement, sampling strategies, retention and loss to follow-up. **Others:** - Given the time provided in the manuscript, it looks like the recruitment should have been finished and now the study is following the participants. It would be very helpful that author presented the recruitment numbers for each site over time as well as demographic characteristics in a Table?

REVIEWER	David Otiashvili Addiction Research Centre - Alternative Georgia, Tbilisi, Georgia
REVIEW RETURNED	24-Jun-2018

GENERAL COMMENTS	This is a well written protocol of the potentially important study investigating the impact of drug consumption rooms on risk practices among people who inject drugs in France. I have few minor comments and points for clarifications. Rationale: • p.7 – in the last sentence authors state that (among other things) PWID are more vulnerable to …lower use of NEP. At least, this is how the sentence reads in its current shape. Please check the wording and revise accordingly to make sure readers clearly understand what you want to say here. • p.8, lines 3-9 – the sentence seems uncompleted and confusing. Please revise • Could you please provide a brief description of any rules or regulations applicable to DCR that might be of interest for the topic of the study, and/or might help readers to better understand the context; for example, what are the criteria for admission? and so on Methods and analysis: • p.9, line 48 – the name of the IRB indicated here seems to be different from the ones mentioned in other places in the protocol. Could you please check which one is correct. • Participants, p.9, line 53 – please provide definition for "regular user" • Measures, p.10, line 17 – you mention "HCV risk practice" here, but in other instances "HCV-HIV risk practice is indicated (for example in statistical methods). Please be consistent with regard to the definition of your main outcome • Measures, 9.10, lines 30-32 – how these injection risk practices differ from those indicated as main outcome (lines 17-19)? • Sample size, p.13, line 9 – please provide definition for DCR-exposed; who will be your "regular" attendees? • Statistical methods, line 36 – you state that the data analysis will be done using regression models for qualitative data. I believe this is an omission and your intention was to use word "quant

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

I would like to thank authors for all their efforts to design and run this important Cohort in France and also drafting the manuscript to share the study methods. I really enjoyed reading the manuscript and have some suggestions and questions for the authors to improve it – they are listed below:

Introduction

The introduction is heavily discussed the history of HIV and response which is not fully relevant but missed two main things to discuss
- The consequences of public injecting and drug use
- The current evidence about safety and efficacy of DCR on risk-behaviors, over-dose and HIV/HCV infections.

We thank the reviewer for these relevant comments. Information about DCR has been added as follows: "**In addition, research on existing drug consumption rooms (DCR) showed that they improve access to primary health care and improve safer injection conditions (Potier, 2014, DAD). By attracting the most marginalized PWID (Wood, 2005, American Journal of Preventative Medicine), they also reduce the level of public injection and so the number of used syringes has dropped in public space (Wood, 2004, CMAJ)**".
With respect to overdoses, we do not expect the DCR to significantly reduce fatal overdoses in France as unlike the situation in North America, the incidence of fatal overdoses among PWID in France is already low. We added a sentence in the introduction to explain the situation: "**Several studies have**

also shown that DCR are effective in reducing fatal overdoses (Marshall, 2011, Lancet).” And also in the discussion: **“In France, incidence of fatal overdoses among PWID is low, making it difficult to reduce it significantly over a 12-month period. This could be related to the national harm reduction policy implemented in the 1990s including access to OST (Emmanuelli & Desenclos, 2005) and a high level of OST coverage (Weill-Barillet et al. 2016, Brisacier 2015).”**

Research objectives and hypothesis

- While in the abstract and the introduction, HIV and HCV have reports as main outcomes of the study, nothing has mentioned about the hypothesis on the association between DCR and the two infections? Although no study has really demonstrated a direct impact of DCR on HIV and HCV prevalence, it has already been shown that DCR have an impact on HIV and HCV risk practices. That is why the main objective of COSINUS is to evaluate the impact of regular DCR use on HIV and HCV risk practices. The hypothesis is that PWID with regular access to DCR have fewer HCV risk practices than those with no access. Furthermore, the length of the follow-up in our cohort (12 months) would not be sufficient to document a direct impact on HCV and HIV prevalence.

- One of the major benefits of DCR is to reduce the over-dose related mortality. This was not mentioned as study outcomes. If there is a plan to measure this effect, details need to be added. If there is no plan, justification need to be provided why it was not measured.
We modified the manuscript as suggested by explaining why the impact on overdoses is not emphasized: “**Several studies have also shown that DCR are effective in reducing fatal overdoses (Marshall, 2011, Lancet). In France, the incidence of fatal overdoses among PWID is already low making it difficult to reduce it significantly over a 12-month period. This could be related to the national harm reduction policy implemented in the 1990s including access to OST (Emmanuelli & Desenclos, 2005) and a high level of OST coverage (Weill-Barillet et al. 2016, Brisacier 2015).**

Study design
- Rational for choosing the two cities for the DCR intervention and also particularly rational for choosing the two control cities need to be provided.
As suggested by the reviewer we added some details: **“These four cities were chosen because they were all candidates for the opening of DCR when the law permitting experimentation with DCR passed (Public Health Law from January 2016).**”

Participant
- What does “regular user” means? Please provide clear definition for it?
This term was not appropriate and we decided to remove it. The main inclusion criteria were clearly defined in the protocol as: “having reported the injection of illegal or/and prescription drugs at least once during the previous month.” We changed the sentence to: “**Subjects were eligible if they reported injecting illicit drugs except cannabis (heroin, cocaine / crack, amphetamines, ecstasy), and/or prescription drugs (methylphenidate, buprenorphine, benzodiazepines, morphine sulphate, oxycodone, methadone) at least once during the previous month**”.

- How injection in last month will be verified? Is it only measured by self-report?
Yes, all the data collected in the COSINUS cohort are self-reported.
- How likely two persons have same “month, year and place of birth” and so records of these two were mixed up?
First, it is very rare that two persons have the same records “month, year and place of birth”. In addition, we have trained field interviewers in each city who are permanently in the different participating harm reduction facilities. As they know the participants very well, it makes it very unlikely that data could be mixed up.

- Not clear of HIV-positive or HCV-negative will be eligible to participate in the cohort?
The reviewer is correct. HIV and HCV statuses are not inclusion or exclusion criteria. However, we asked the participant to self-report their serostatus. We added this data to the “data collection“ section as follows: …HIV, HCV and HBV screening **and self-reported HIV and HCV status, …**

- Is there any condition that make participants ineligible for study, i.e. what are the exclusion criteria?

There are no specific exclusion criteria, except if the PWID does not fulfil the inclusion criteria. The only important exclusion criterion to be noticed is that non French-speaking PWID are excluded who represent until 20% of people who attend harm reduction facilities in some sites.

Key exposure measurement

- It looks like the enrolment in the cohorts are DCR sites in the two cities that have DCR sites and from other harm reduction sites in the two cities that do not have DCR sites.

This is true except that in cities with a DCR, PWID are recruited mainly in the DCR *and* in other harm reduction facilities close by when possible. We added a sentence to provide more details **"They [the participants] were recruited mainly in the DCR (in the cities where there is one) and in other harm reduction facilities that currently outreach to PWID likely to attend a DCR if available in each city. This mix of recruitment sites was chosen in order to be able to compare PWID between cities."**

- And then in the measurement section, DCR exposure was measured by questionnaire and self-report which is not a perfect way. I am wondering why it is not measured by linking the records at DCR to study participants by some links like date of birth etc.

As suggested by the reviewer, it would have been very interesting to match data from the DCR to data from the cohort. However, it was not feasible because of different reasons: the evaluation of DCRs started when DCRs just opened and it would have been very complicated for them to add a research activity to their operational activities. Moreover, to collect data in the same way from the different harm reduction facilities and to have a more reliable perception from PWID, we decided to have independent interviewers with specific questionnaires. Finally, French regulations make possible by law for attendees to not reveal their identity or other personal information and it is important to respect this right for participants.

Sample size

- What does "regularly attend" means in the following statement: "different countries with DCR have shown that between 30%36 37 and 60%38 of users regularly attend them"

Regular attendance means "having attended the DCR at least once a week." We added this information to the statement as follows: …**regularly attend them (at least once a week).**

- Based on what the sample size allocated to the four cities?

We estimated the number of participants to be recruited on the basis of French data showing the numbers of PWID of each participating site on the project.

Statistical analysis:

- It was not clearly mentions how the "combined effect" of DCR together with other HR services will be assessed? How this combined effect will be developed and what model will be used to assess it?

To study the impact of the combined effect we will take into account the exposure of participants to DCR, needle exchange programs, education to safer injection and other services. We added a sentence to explain this in the statistical analyses: "**In addition, to study the impact of the combined effect of different services (DCR, education about safe injection, other HR services) on the main outcome, we will use mixed-model regression analysis by adjusting for these different structural factors and other covariates.**"

- It was not clear how the loss to follow up will be assessed and analysed: We thank the reviewer for this comment. We added a relevant sentence to the statistical analyses section: **"To take into account bias due to missing data and loss to follow-up, we will perform sensitivity analyses using the Heckman model, which adjust for this potential source of statistical bias (Carrieri et al, 2006, JAIDS)."**

Discussion:

- I am wondering if study has any limitation that need to be acknowledged like self-report measurement, sampling strategies, retention and loss to follow-up.

There are several limitations and we omitted to add this section. Thank you for this suggestion. A "Limitations" paragraph has been added as follows: **"Some limitations have to be acknowledged. First, all the data collected were self-reported. Although the use of self-reports may be subject to social desirability bias, studies have shown their reliability in drug-using populations (Darke, 1998, DAD, Denis 2012, DAD). To control any such bias, we used trained interviewers**

independent of the participating harm reduction facilities. In terms of the diversity of our sample, all the PWID were recruited through easily accessible harm reduction facilities which conduct outreach actions, and which constitute the main contact that the PWID population has with the health care system. Another limitation is that, due to cost limitations of our study, we enrolled only French-speaking participants. Further studies are planned to better investigate the impact of DCRs in all the population of PWID including non French-speaking PWID that represent around 20% of people who attend DCRs in certain sites (Jauffret-Roustide et al. 2017)."

Others:
- Given the time provided in the manuscript, it looks like the recruitment should have been finished and now the study is following the participants. It would be very helpful that author presented the recruitment numbers for each site over time as well as demographic characteristics in a Table?
Yes, the recruitment for the enrolment phase of the cohort has just finished but the data have not been analysed. These data will be presented in a next article. In the present article, we simply wish to describe the protocol.

Reviewer 2

This is a well written protocol of the potentially important study investigating the impact of drug consumption rooms on risk practices among people who inject drugs in France. I have few minor comments and points for clarifications.

Rationale:
- p.7 – in the last sentence authors state that (among other things) PWID are more vulnerable to …lower use of NEP. At least, this is how the sentence reads in its current shape. Please check the wording and revise accordingly to make sure readers clearly understand what you want to say here.

- p.8, lines 3-9 – the sentence seems uncompleted and confusing. Please revise

The reviewer is correct. As this section was not very clear and did not add important information, we decided to remove it.

- Could you please provide a brief description of any rules or regulations applicable to DCR that might be of interest for the topic of the study, and/or might help readers to better understand the context; for example, what are the criteria for admission? and so on
We thank the reviewer for this remark. We added the following sentence: "**These two DCR accept all PWID 18 years or older and provide the following services: the possibility to administer drugs by injection (or inhalation in some cases, only for PWID), access to social, medical and psychiatric consultations, the provision of sterile equipment, the collection and disposal of used injection equipment, primary care, harm reduction counselling and HCV, HBV and HIV testing."**

Methods and analysis:
- p.9, line 48 – the name of the IRB indicated here seems to be different from the ones mentioned in other places in the protocol. Could you please check which one is correct.
We corrected the name of the IRB in the article as follows: "**The study protocol was approved by the Institutional Review Board (IRB00003888) of the French institute of medical research and health (opinion number: 14-166)."**

- Participants, p.9, line 53 – please provide definition for "regular user"
This term was not appropriate and we decided to remove it. The main inclusion criteria were clearly defined in the protocol as: "having reported the injection of illegal or/and prescription drugs at least once during the previous month." We changed the sentence to: "**Subjects were eligible if they reported injecting illicit drugs except cannabis (heroin, cocaine / crack, amphetamines, ecstasy), and/or prescription drugs (methylphenidate, buprenorphine, benzodiazepines, morphine sulfate, oxycodone, methadone) at least once during the previous month**".

• Measures, p.10, line 17 – you mention “HCV risk practice” here, but in other instances “HCV-HIV risk practice is indicated (for example in statistical methods). Please be consistent with regard to the definition of your main outcome
As suggested by the reviewer, we standardized the term using **HIV-HCV risk practices**.

• Measures, 9.10, lines 30-32 – how these injection risk practices differ from those indicated as main outcome (lines 17-19)?
These risk practices include more items not only related to injection. That is why we changed the wording of our main outcome by using: **injection-related HIV-HCV risk practices.**

• Sample size, p.13, line 9 – please provide definition for DCR-exposed; who will be your “regular” attendees?

We better defined what is regular attendance in the sample size section as follows: “Regular attendees are those attending DCR at least once a week. We clarify this as follows: “We hypothesize 33% of **regular (i.e., at least once a week) DCR attending participants will report at least one of these events**.”

• Statistical methods, line 36 – you state that the data analysis will be done using regression models for qualitative data. I believe this is an omission and your intention was to use word “quant
The reviewer is correct and we removed the words “for qualitative data”.

VERSION 2 – REVIEW

REVIEWER	David Otiashvili Addiction Research Centre - Alternative Georgia, Tbilisi, Georgia
REVIEW RETURNED	11-Oct-2018

GENERAL COMMENTS	Authors addressed all the concerns and questions raised during the review. I have no additional comments.