Mobile treatment units for medication-based treatments of Opioid Use Disorder

An epidemiology study design project

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1 Study Description

I propose a study of the impact of mobile treatment vans for methadone delivery to people with opioid use disorder (OUD). A large body of evidence spanning decades supports the use of Methadone (also called Methadone and Dolophine) for treatment of OUD [1]. Despite this, the majority of people suffering from the disorder do not get medication-based treatment [2]. By law Methadone treatment can only be conducted by specially-licensed practitioners and those in treatments are required to report to the clinic every day to get the treatment, at least initially [1]. These policies have been implicated as barrier to treatment [3]. The start of the pandemic caused a wave of logistical restructuring across field, including healthcare, and the use of mobile treatment units (MTUs) that can bring medications to people by van was considered as an option to improve access[4]. A growing line of research asses the effectiveness and feasibly of this treatment modality[5].

2 Scientific Question (Assn. 1)

Study Design Assignment 1: Matching your scientific question to the best study design and preventing information bias. Provide a concise but complete response (At least 2, but not more than 4 pages) to the following questions.

a. Do mobile treatment units for Methadone increase the access to care for people with OUD? This might be hard to asses but I think it's worth coming up with something because it's really the core of effort to get better treatment to more people. Sub-question: does this results in fewer adverse events?

b. Do mobile treatment units change the demographics of people receiving methadone? The demographics of the opioid epidemic are complex and have shifted since it began with working class in whites in deindustrialized areas making up the majority of cases and other groups becoming more involved more over time. Monitoring for demographic shifts could help asses if the programs were helping in a fair way.

c. Do mobile treatment units results in fewer cases of COVID among people with OUD? One think worth interrogating is if switching to the vans would help at all. If not, it might make sense to divert resources back to the initial clinics. If it reduces infections, it could serve as a treatment model for other diseases.

2.1 Choose one of the scientific questions that you have proposed above and answer the following questions. (Though you may change your study question later)

a. What is your conceptual exposure? Is this exposure rare or common?

My exposure is opioid use disorder in a region where MTUs are being explored as a potential treatment delivery system. It's rare compared to something like cardiovascular disease, and I don't think it's greater than 20% of the population (the rough rule we're using for this class) [double check]. It is increasingly common however, having become the leading cause of accidental death [find where I read this].

b. What is your conceptual outcome? Is this outcome rare or common?

The outcome would be receiving medication-based treatment for opioid use disorder via a MTU (let's say, >10% of the time)[note: might need to workshop this]. It would also make sense to track adverse events like hospitalizations, overdoses, and deaths.

c. Briefly describe how you might use each of the four major study designs in epidemiology (cohort, case-control, cross-sectional (or ecologic if you like), or randomized trial) to assess this question. For purposes of this exercise, I'd like you to stretch your ideas about study design, so do your best to come up with a way to use every one of the study designs to address your question of interest. Feel free to be a bit creative for this part of the question (you will assess feasibility and logistics in the next part of the question).

- Cohort: In this design, we could enroll people based on their opioid use disorder status and the policy of the closets methadone clinic (if they use vans or not). After the enrollment, we would follow them for a designated period. We could then asses a variety of metrics like adherence, overdoses, or death. The main one would be adherence, defined as people who reported to the van. We could then compare this to the rates in the people who didn't have the van option. This would be the prospective option. For the retrospective version, we could attempt to find data on overdoses, demographics, etc from historical database. We could then see if people in the MTU regions different in terms of endpoints.
- Case control: This ones stretches my proposal quite a bit. I need to think on it [return to this]. In this we would need to define a different endpoint, let's say overdose. We could enroll people in a non-MTU region as controls and a MTU region as cases. We could follow them and see if they different on our endpoints. OUD is likely uncommon enough that odds ratio would approximate the risk.
- Cross-sectional: In this method, we might obtain interview or medical records. We would asses the desired information on demographics and outcomes. We could review the records to see if subjects had an overdose, etc. The advantage here is that it's the cheapest and fastest. The downside is that we wouldn't have continuity in terms of time and would have very little control over confounding.
- Randomized trial: In this version of the study we would randomly assign people to treatment regions where MTUs were available and some to those where they weren't. This would be extremely difficult logistically because the point of the MTUs is to address access, and assigning people to facilities other than the closest one would be prohibitive. Perhaps it would be possible to assign the MTU programs randomly as pilot programs instead of using the places where it was already in use.

2.2 Focus in on what is pragmatic or logistically possible to answer the following questions about your scientific question and study design.

a. Which study design from part 2c seems most feasible? Why does this design seem best for addressing your scientific question?

I think there are two that could work here, the cohort and the cross-sectional study. The cohort would be more ambitious - it would require following people who might be at higher risk for housing instability over a long period of time if the prospective option was used. If the data were available already, it could be approached retrospectively. This might be the most practical option in terms of balancing feasibility with robustness.

The cross-sectional might be the best we could do if the data were only available as a snapshot.

b. What will you use as your operational exposure and outcome? Or what are some reasonable options for operational exposure and outcome? Note that this should match up to the study design you've identified as most feasible in 3a.

Let's assume we can do a retrospective cohort study. In this case the operational exposure would be a medical record reporting use of illegal opioids. The patients would then be categorized as having used a MTU for medical treatment of OUD or having used a traditional clinic. The outcome would be reporting to the ER with an overdose or a fatality.

c. What other data will you need to collect for you study (i.e., what are the important covariates for your study)?

Given the complex demographic makeup of the opioid crisis[2], it would be crucial to collect information such as race and sex, and given the variation in risk with employment and education, information on work and schooling. Geographic information may be required as well.

2.3 Place your chosen question into the broader context of the existing literature.

a. Identify 2-4 relevant papers from the primary literature to provide background and motivation for your proposed study. Provide the citations and a 1-2 sentence summary of the critical background information contained in each study.

Joudrey PJ, Edelman EJ, Wang EA, "Methadone for Opioid Use Disorder—Decades of Effectiveness but Still Miles Away in the US" [1] provides evidence of the effectiveness of methadone as well as background on the restrictions around using it. It also contextualizes status quo by discussing the political and policy factors that created it.

Cerdá M, Krawczyk N, Hamilton L, et al, "A Critical Review of the Social and Behavioral Contributions to the Overdose Epidemic" [2] provides and exhaustive overview of epidemic with a focus on the demographic and policy aspects. It also includes a history of the epidemic and an analysis of economic drives of supply and demand of drugs.

Jakubowski A, Fox A, "Defining Low-threshold Buprenorphine Treatment" [3] specifically discusses the barriers to entry in pursuing medication-based treatment for OUD. It's main contribution is a definition of and argument for treatment policies that emphasize making treatment more easy to get.

Chan B, Hoffman KA, Bougatsos C, et al "Mobile methadone medication units: A brief history, scoping review and research opportunity" [5] describes the history of mobile treatment units. It also lays out the case for using them as an opportunity to asses drug-based treatments. In particular, because they are becoming legal and being tested, we will now when the change was adopted for comparison.

b. What knowledge gap does your proposed study address? (i.e., Will it add to our scientific knowledge by answering a completely new question? Will it help us understand a new mechanism to explain a previously observed association? Will it extend the research to a new population?)

My proposed study would asses the demographics of those who seek medication-based treatment for OUD in a mobile setting. This would offer insights into what communities benefit the most, if there is a disparity. This would highlight needs for future work. If the vans are broadly effective and demographics do not show a disparity, it would confirm their value. It could also interrogate the utility in improving outcomes. The demographics would be a new contribution as would the outcomes. The benefit of medication assisted treatment in general is well established and would not be a contribution.

2.4 Are there any relevant sources of information bias to consider for your study as designed (consider all potential types of information bias)? How might you prevent these or improve exposure/outcome/covariate data collection to minimize these concerns?

There are numerous ways this study could be impacted by information bias.

2.4.1 Recall Bias

If we were to pursue the cross-sectional version of the study this would likely be a large issue. Given that opioids influence the mind there might be issues in recalling if, when, and how many non-fatal overdoses occurred. We could restrict to participants with medical records going back a certain amount of time to help with this.

2.4.2 Interviewer Bias

The interviewer bias would be more likely if we chose the cross-sectional version of the study. In this situation an interviewer might be more likely to assume people with certain traits are more likely to be drug uses and ask leading questions accordingly ("Are you sure there weren't more?", etc). We could address this by automating simple interviews (ie, using some kind of survey tool).

2.4.3 Loss to follow up

If we were to pursue a cohort study, we might have issues if people having moving or transferring care facilities. In particular, given that housing instability is likely higher among people who use drugs, it could be hard to follow up with people with no permanent address. Given that opioid use is criminalized, people could be arrested before the study is complete. I think this would be one of the biggest threats to the study in practice if we did the cohort version. We might be able to ameliorate the address by only enrolling people with a legal address though this would cost us in terms of generalizability. In terms of the legal issues there isn't a lot we could do.

2.4.4 Misclassification of exposure or outcome

This could manifest in terms of counting overdoses. Someone could take a dangerous amount of a substance and not die but not report to a hospital. This "close call" should, in theory, constitute an overdose in terms of risky behavior, but would not appear on a medical record. This is exactly the kind of thing that gets underestimated in epidemiological studies. Correcting it sully is likely impossible. We could probably not change it but we could consider the effect it would have when interpreting the results. For example, this effect often biases towards the null.

3 Confounding (Assn. 2)

Study Design Assignment #2: Creating a strategy for the control of confounding

Provide a concise but complete response (1-2 pages) to the following questions.

I am interested in assessing the effect of mobile treatment units for methadone treatment of opioid use disorder. In particular I'm interested in seeing if there are fewer adverse events when they are utilized (death, hospitalization, overdoses). Lastly I am interested in noting any demographic shifts in the people getting treatment when they are used as people in rural areas are not always able to make it to more centralized urban clinics. This could inform holistic treatment policies in that knowing, for example, rural and urban populations get treatment differently.

3.1 Based on the papers that you reviewed for Questions 3 & 4 in Exercise 1, list the important potential confounders of your exposure-outcome association. Will any of these be particularly challenging to measure?

One variable that's a concern based on my DAG is baseline opioid burden/usage. I think if it's higher the risk is greater to a given person, but it would also probably influence treatment. Thus, I'd need to adjust for it. Socioeconomic status also comes up a lot in the papers, as do race and education levels.

3.2 How might you integrate prevention or control of confounding into your study design or analysis?

I think for my study it makes sense to focus on controlling in a multivariate analysis. I don't want to rely too heavily on restriction because I'd like to generalize to more than one region or population. That said, I'd do if it there turned out to be a reason to. For instance, if I were to find that there were a lot of clinics in the cities it might might make sense to limit to rural areas as the need was already met.

3.3 Based on your answers in part 3 and 4 of Study Design Assignment 1, create a preliminary DAG...

...to define set {S} to describe which confounders you may wish to include in a multivariable model. You may use Daggity, R, Powerpoint, etc., to make your DAG. A clear and legibly hand drawn DAG is also acceptable. (Note: If you chose a randomized trial, please use the DAG to help you describe the confounding structure that will be accounted for via randomization).

Let:

- Age = Age
- FO = Fatal Overdose
- O = Opioid use rate of the region
- Tx = Treatment (Mobile available or not)
- Edu = Education level
- Geo = Geographical location/residence
- Sex = Biological sex
- SES = Socioeconomic status
- Emp = Employment

Most of these should be fairly available depending oh how granular federal overdose data are. I think county-level stats are accessible at this point.

```
library(ggdag)
```

```
Attaching package: 'ggdag'
```

```
The following object is masked from 'package:stats':

    filter
```

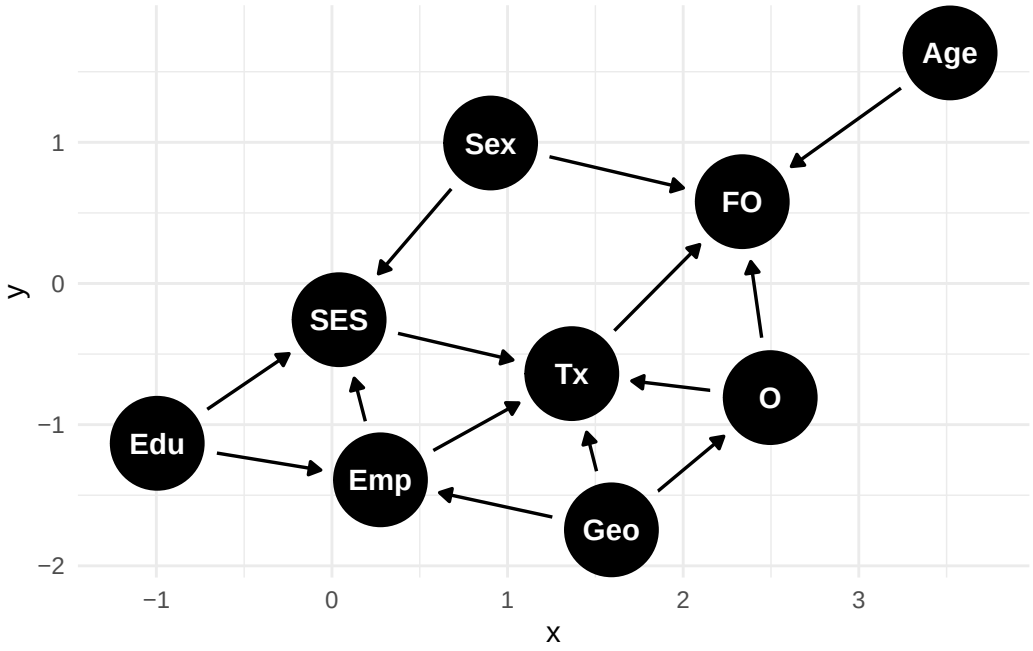
```
library(ggplot2)

g <- ggdag::dagify(
    Tx ~ Geo,
    Tx ~ SES,
```

```
    Tx ~ Emp,
    Tx ~ O,
    FO ~ O,
    SES ~ Emp,
    Emp ~ Geo,
    FO ~ Tx,
    FO ~ Age,
    FO ~ Sex,
    SES ~ Sex,
    O ~ Geo,
    Emp ~ Edu,
    SES ~ Edu

)

ggdag(g) +
    theme_minimal()
```



My set S would thus be $S = \{O, Geo, Emp, Sex, Age\}$

Most of these should be fairly available depending oh how granular federal overdose data are. I think county-level stats are accessible at this point.

3.3.1 a. Describe/define each individual component in the DAG.

Let:

- Age = Age (in years)
- FO = Fatal Overdose (a death that was ruled to be overdose-related)
- O = Opioid use rate of the region (deaths per time period in the region where the subject is)
- Tx = Treatment (Mobile treatment available or not)
- Edu = Education level (No HS, HS, College, Postgrad)
- Geo = Geographical location/residence (Where the patient lives)
- Sex = Biological sex (the biological sex of the patient)
- SES = Socioeconomic status (Lower, Middle, Upper, bracket of household income)
- Emp = Employment (has the person worked 36+ hour a week for the last 6 months)

3.3.2 b. Was it difficult to assess directionality of any of the arrows? What additional information would you like to have

```
>(Note: The goal is not necessarily to produce a perfect and final DAG,
but to help you gain an appreciation of the importance of this step and
some of the challenges in DAG creation. You need not do a full literature
review to support your DAG, but do use information from the papers identified
in part 4 of assignment 1 to help you identify potential confounders and
inform your DAG.)
```

Yes - I think it's hard to say if race "causes" geography or the other way around since they don't cause one another say but the geographic location of the survey does impact the chances of a given subject being a particular race. Mostly it wa hard to avoid a few bidirectional arrows.

4 Selection, sample size, participant burden (Assn. 3)

Study Design Assignment #3: Preventing selection bias, identifying a source population, estimating sample size, and understanding participant burden

Provide a concise but complete response (2-3 pages) to the following questions.

I am interested in assessing the effect of mobile treatment units for methadone treatment of opioid use disorder. In particular I'm interested in seeing if there are fewer adverse events when they are utilized (death, hospitalization, overdoses). Lastly I am interested in noting any demographic shifts in the people getting treatment when they are used as people in rural areas are not always able to make it to more centralized urban clinics. This could inform holistic treatment policies in that knowing, for example, rural and urban populations get treatment differently.

4.1 Precisely how might selection bias occur in the type of study you are designing (e.g., what causes selection bias in a case-control study)?

This is a cohort study interested in regions. In comparing different regions, these studies carry a risk subjects are counted differently (more on this in the next question). Cohort studies are also vulnerable to any issues that come with a lack of randomization. For example, if you use phone calls to collect participants and call during business hours, you're skewed towards households where one adult might not have to work and that still have a landline (presumably older and more economically secure than the general population).

4.2 Based on your study design and chosen source population, describe any relevant considerations for preventing selection bias in your study (i.e., how might selection bias occur specifically in the study that you have designed?).

One issue with studying drug overdoses is a lot of drug overdoses occur from mixing drugs. If opioids and cocaine are both present in blood samples, for instance, this this could be seen as a incident for those who study either. Some also argue this increases the counts attributed to opioids. If one region in my study had a lot "polydrug" use, as it is know, and those weren't counted, this could impact our findings (the manner in which this would impact the study would depend on which research question).

4.3 What would be the ideal source population or data source for this study? Why?

The ideal would be data collected and standardized by a public health institute or organization. There would be data from several states and from rural as well as urban settings (though it would likely skew rural as cities are more likely to have centralized clinics in densely populated areas and more access to public transport). The goal would be to keep the study as generalize as possible because the issue is of national, not regional concern. It would also be interesting to see if the mobile units changed the demographics of the people who got treatment. If we only studied majority-white areas this would be difficult.

4.4 Identify and briefly describe 2-3 real data sources (e.g., NHANES, Danish National Registry, etc.) or populations (e.g., patients at DHMC, workers in a specific industry, etc.) that you might target for this study. Which of these seems most useful for your particular study?

Most of the resource that are readily available are from specific CDC programs.

- Overdose Data to Action, which is concerned with overdoses in general and is particular with risk factors associated with risk.
- Youth Risk Behavior Surveillance System which tracks risky behaviors in young people, including alcohol and drugs.

- A 1996 study, *Patient retention in mobile and fixed-site methadone maintenance treatment*, which was done with data collected via interview [6]. This would be the most specific.

The first two would be useful for context and summary stats, but the last is the only one I could find with data on the mobile treatment units. Given the DEA changes took place in the last few years, it's not surprising it's hard to find.

4.5 Based on associations observed in prior studies, what is your sense of how large your study will need to be (100, 1000, 10,000, 100,000)? Perform a power or sample size calculation for you study. A helpful module on this topic is available at: http://sphweb.bumc.bu.edu/otlt/mph-modules/bs/bs704_power/BS704_Power_print.html

The study mentioned above [6] had 399 + 1588 = 1987 subjects. I think this would probably be good for mine as well but let's confirm.

4.5.1 Assuming comparing means

If I ended up using counts of deaths in several regions and wanted to compare average deaths between the van available and unavailable groups, I could go with an ANOVA.

```
library(pwr)

pwr.anova.test(
  # standard power
  power = 0.8,
  # vans available yes/no
  k = 2,
  # gotta start somewhere
  n = 20,
  # standard
  sig.level = 0.05
)
```

```
Balanced one-way analysis of variance power calculation
```

```
              k = 2
              n = 20
              f = 0.4545483
      sig.level = 0.05
          power = 0.8

NOTE: n is number in each group
```

I'd be counting on a fairly high effect size with these numbers. Given what they saw in Greenfield, et al[6] though, I might be able to get away with it.

4.5.2 Assuming a hazard ratio approach

Let's also consider a longitudinal approach:

```
library(survivalpwr)

pwr_coxph(
  # assuming this effect size as a starting points
  hr = 1.5,
  # we'd need to tweak this based on the literature but let's assume
  # there is something like a 10% probability of overdose
  eventprob = 0.1,
  # based on the aforementioned study
  n = 1987
)
```

```
   Cox Regression power calculation

            n = 1987
      nevents = 198.7
           hr = 1.5
    eventprob = 0.1
      rsquare = 0
       stddev = 0.5
    sig_level = 0.05
        power = 0.8153477
  alternative = two.sided
```

4.6 Review Lingler et al. 2015 and the related Perceived Research Burden Assessment tool for a description of direct (e.g.,) and indirect (e.g., inconvenience) burdens potentially experienced by research participants : https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4487419/.Consider both direct risks and indirect burdens, and describe what will be the participant burden for subjects in your study?

This study would be difficult to do in a lot of ways, but would be relatively mild in terms of participant burden. We'd mostly be following people who where in treatment to note their status at the end. They would not have to change a behavior, take an experimental drug, etc, thus it would be quite a manageable study from a direct burden standpoint.

One thing that would be a concern is time. They would need to remain in the study for a non-negligible amount of time. This would be an indirect burden.

4.7 Are there any ethical concerns to consider in working with your population of interest? (Hint: if your study involves human subjects (or their data), then the answer is yes. If you have not completed training in the protection of human subjects, you may wish to briefly familiarize yourself with the NIH policies related to the protection of human subjects: https://grants.nih.gov/policy/humansubjects.htm.) Does your research use vulnerable populations or others requiring special protections (this specifically relates to the following NIH policy: https://grants.nih.gov/policy/humansubjects/policies-and-regulations/vulnerable-populations.htm)?

There are, of course, some concerns. The largest is the sensitivity of the data. People who use drugs may face significant stigma. If their identities were compromised, this would be a significant ethical failure of the study. Depending on the details, my study might qualify as involving a vulnerable population. Some opioid research involves people who are incarcerated.

References

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2 Cerdá M, Krawczyk N, Hamilton L, *et al.* A Critical Review of the Social and Behavioral Contributions to the Overdose Epidemic. *Annu Rev Public Health* 2021;**42**:95–114. doi:10.1146/annurev-publhealth-090419-102727

3 Jakubowski A, Fox A. Defining Low-threshold Buprenorphine Treatment. *J Addict Med* 2020;**14**:95–8. doi:10.1097/ADM.0000000000000555

4 Krawczyk N, Fingerhood MI, Agus D. Lessons from COVID 19: Are we finally ready to make opioid treatment accessible? *J Subst Abuse Treat* 2020;**117**:108074. doi:10.1016/j.jsat.2020.108074

5 Chan B, Hoffman KA, Bougatsos C, *et al.* Mobile methadone medication units: A brief history, scoping review and research opportunity. *J Subst Abuse Treat* 2021;**129**:108483. doi:10.1016/j.jsat.2021.108483

6 Greenfield L, Brady JV, Besteman KJ, *et al.* Patient retention in mobile and fixed-site methadone maintenance treatment. *Drug and alcohol dependence* 1996;**42**:125–31. doi:10.1016/0376-8716(96)01273-2