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Commentary on Sordo et al. (2015): Reducing bias in prospective observational studies of drug users: The need for upstream and downstream approaches

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Concise Statement

The finding by Sordo et al., of a strong relationship between incidence of injecting initiation and length of follow up draws attention to selection bias caused by greater attrition among those at higher risk. We highlight the need for closer attention to upstream, as well as downstream approaches, when designing and implementing prospective observational studies.

Bias in clinical and epidemiological research results from systematic error in the design or conduct of the study and this error implicates the validity of results. Systematic error results from flaws in either the (1) method of selection of study participants, or (2) in the procedures for gathering relevant exposure and/or outcome information [1]. Selection bias can occur when individuals have different probabilities of being included in the study according to relevant study characteristics: namely the exposures and or the outcome being studied. In cohort studies, the most common form of selection bias occurs with loss to follow up. When those lost to follow up are more or less likely to include exposed and affected individuals (differential loss to follow-up), the probability of the outcome is different in those who remain in cohort vs. those who are lost. This kind of selection bias is the known Achilles heel of prospective cohort studies. The potential for differential loss to follow up and its nemesis bias is compounded in studies of marginalized and vulnerable populations such as drug users and homeless people.

The study by Sordo et al. [2] provides the first review and meta-analysis of prospective observational cohort studies on initiation into drug injection among vulnerable populations. The major finding was a strong relationship between the incidence of initiation to injecting

and the length of follow up time. As the authors note, the strong decline in the incidence of initiation of drug injection observed with increasing follow-up time is suggestive of a severe downward selection bias (toward primarily low-risk participants) caused by greater loss to follow-up among individuals at higher risk of initiating injection. A more elevated risk of injection or death among those lost compared to retained participants would also lead to an increasing portion of low-risk individuals being retained over time, resulting in biased estimates of incidence of injection initiation.

Sordo et al. [2] present a thoughtful discussion of how selection bias resulting from outcome-related loss to follow-up can bias results and a well-articulated presentation of how to correct for this using new analytic techniques - such as inverse probability weighting for marginal structural models (MSM). These techniques are gaining ground and offer great potential to address bias analytically by quantifying the amount of error and presenting 'corrected' and potentially more 'valid' estimates of excess risk. As they note: "All the reviewed studies assessed attrition bias by comparing participants with at least one visit to non-retained participants. The information provided by this exercise is inconclusive (Table S3). Likewise, the follow-up figures do not allow assessment of losses in appropriate follow-up intervals" (insert page number). The MSM methods which are now available offer important methodological improvement in the field and can contribute to better and more valid estimates, however, these approaches are principally 'downstream' methods.

Good public health science also necessitates attention to 'upstream' factors. The potential for bias also needs to be addressed in the earliest stages of planning and executing a cohort study, not just the analytic stage. Prospective observational studies are among the hardest to implement without extensive planning and thought apriori. As Sordo et al. [2] note "Retaining and tracking illegal drug users in cohort studies is difficult and requires many special procedures during study implementation" (insert page number). We cannot analyse our way out of conducting good science – from its inception.

Many researchers planning prospective observational studies use selection criteria such as planned mobility, or techniques such 'run-in' periods to target participants who are likely to be able to participate over a long time period to reduce loss to follow up. If these criteria are associated with the outcome – for instance, injection initiation, this could also bias results. There are now new technologies and methods available to enroll and follow cohort participants. Studies are increasingly using social media [3, 4], peer-contacts and support [5], internet, smartphone and SMS technologies [6, 7], and even GPS devices [8]. These new methods offer important upstream opportunities and approaches to minimizing bias.

Rates of initiation to injecting and associated factors are important to study and critical for the identification of windows of opportunity for prevention interventions. A large number of the studies (4/9) included by Sordo et al. [2] were in a population with known risk of loss to follow up – homeless or unstably housed people. Today, we have new populations initiating injecting, including young people who are transitioning to injecting following initial oral use of pharmaceutical opioids (PO) [9, 10]. In the U.S. there is a significant and growing group of PO users with apparent transition from oral to injecting administration of opioids,

typically within 2–3 years of initiating use [10–12] with associated outbreaks of hepatitis C virus infection [13] and now one of the most serious HIV outbreaks in recent history [14].

However, the dynamics of these transitions and the factors which predict initiation of injection in this group remain largely unknown. Given the alarming rise in PO use among young people throughout North America and the potential for this to lead to unparalleled levels of opioid dependence and injection drug use, and associated epidemics of infectious disease, there is an urgent need to scale up evidence-based prevention programs, including drug treatment, HIV and HCV testing access, syringe availability through harm reduction programs and pharmacy sales, and naloxone to prevent overdose. Improved access and coverage of these programs will also help us to conduct better public health research – as drug users will be accessible and less likely to disappear – resulting in data than can truly and *validly* inform future public health responses.

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