TITLE: COMPARING TRIAL DESIGNS FOR HCV TREATMENT AS PREVENTION: AN EMPIRICAL EVALUATION

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Background Theoretical studies predicted treatment as prevention (TasP) impact of scaled-up HCV treatment to people who inject drugs (PWID), but no empirical evidence exists and the ideal evaluation design is unclear. To inform trial design, we compare statistical characteristics TasP trial designs utilizing UK surveillance data.

Methods We performed a simulation study based on UK surveillance data to compare two potential HCV TasP trial designs among PWID: observational study of intensive scale-up in a single site compared to a cluster randomized control trial(RCT). Dynamic modeling predicted HCV chronic prevalence among PWID with/without treatment scale-up. For the observational study (as planned in Dundee, Scotland), 500 additional treatments across 2 years were simulated in Dundee, and a modified (error-in-variables) synthetic control approach was used to assess statistical power to detect simulated intervention effect. For comparison, a cluster RCT across 4 sites (similar to Dundee, East London, Nottingham, Plymouth) was simulated.

Results In Dundee, modeling predicts chronic prevalence among PWID will drop by a relative 19% from 2017-2019 without scale-up, and by 70% with an additional 500 treatments (64% relative reduction in 2019 with intervention compared to standard-of-care). A modified synthetic control approach achieves 79% power to detect the cumulative intervention effect assuming strong correlation between the outcome in Dundee and controls. By comparison, while randomization protects against confounding, a cluster RCT distributing 500 treatments across 4 UK cluster sites achieves <25% power to detect the effect. To achieve 80% power using a cluster RCT, 10-fold increase in surveillance sample sizes or 1020 treatments are required. Both approaches controlled false positive rate near the nominal 5%.

Conclusions An intensive single-site intervention and modified synthetic control analysis achieves good power to detect a TasP effect in Dundee. A cluster RCT design requires substantial investment in enhanced surveillance and/or more treatments to achieve similar power.