Program Refinements to Optimize Model Impact and Scalability Based on Evidence (PROMISE)

NCT03628287

Date: July 27, 2020

Study Protocol and Statistical Analysis Plan

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The full protocol has been previously published.[1] Excerpts are provided below.

Eligibility criteria (for clients and sites)

PWH eligible for the trial analysis of CCR intervention effects include those newly enrolled in the CCP or CCR and having unsuppressed VL (HIV RNA ≥200 copies/mL) as of their latest test in the year prior to enrolment or having no VL test result reported to surveillance in the year prior to enrolment (presumed out of care).[10] To allow 4 months of VL outcome observation per enrollee prior to the start of the next phase of CCR rollout, the trial-eligible enrolment window for each 9-month implementation period is restricted to the first 5 months. The trial excludes newly awarded (CCP-naïve) agencies and includes only the 17 re-awarded agencies, which could be assigned to continue CCP delivery uninterrupted or begin CCR delivery in the initial implementation phase.

Outcome measurement

To assess the clinical benefit of the programmatic revisions distinguishing the CCR from the CCP, we will analyze client-level, surveillance-based laboratory test data.[10] The outcome, timely VS (TVS), is defined as VL <200 copies/mL on the last VL test reported to the NYC HIV surveillance registry in the 4 months following CCP/CCR enrolment (TVS=1). We have chosen to dichotomize VL data for statistical analysis using the cut-off value of 200 copies/mL, in accordance with the CDC definition of VS.[24] Consistent with our prior CCP work,[8 10 11 18] those without any VL measure during follow-up will be considered not to have achieved VS (TVS=0), given their lack of documented clinical monitoring since their last unsuppressed VL. The 4-month follow-up period aligns with US Department of Health and Human Services HIV guidelines, which reinforce the standard practice of VL monitoring every 3 to 4 months, or more often when adherence difficulties are apparent.[25] For PWH starting ART or a modified ART regimen, the guidelines recommend VL monitoring every 4 to 8 weeks until VS is reached, and state that 'individuals who are adherent to [ART] and do not harbor resistance mutations to the component drugs can generally achieve viral suppression 8 to 24 weeks after ART initiation.'[25] Recent publications also support the applications of shorter-term measures of VS; researchers at NYC's Health Department have proposed adding a 3-month VS indicator for tracking national progress on the HIV care continuum,[26] and a San Francisco study of a vulnerable population of newly diagnosed patients referred for rapid ART initiation found that the median time from start of ART to VS was 41 days.[27] Our TVS measure takes into account both the timing of routine VL monitoring in as-yet-unsuppressed PWH and current expectations for VS achievement in a context of effective ART and universal/immediate treatment policies.[25 28 29]

Timeline

Figure 1 illustrates the three 9-month periods used in the stepped-wedge design: Period 0, with CCP at all 17 agencies and no CCR; Period 1, representing CCR implementation only at sites randomized to an early start (and thus encompassing the months of simultaneous operation of the CCP and the CCR); and Period 2, representing CCR implementation at all 17 sites.

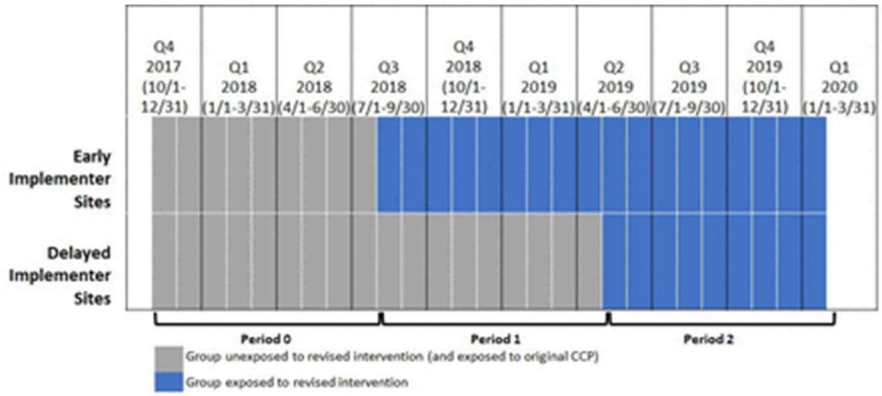

Figure 1: Stepped-wedge design with three implementation periods. CCP, Care Coordination Program.

Recruitment

Beyond standard contract startup deliverables based on early program enrolment milestones, no specific incentives have been used to encourage recruitment. Analyses will include all eligible enrolments in CCP/CCR services at any of the 17 study sites.

Assignment of interventions

Randomization

Though the unit of analysis for TVS is the individual, the unit of randomization is the Care Coordination provider agency (i.e., cluster). Cluster randomization serves to minimize crossover between intervention conditions and avert the logistical and ethical dilemmas posed by client-level randomisation.[30–32] Agencies were matched and randomized within pairs (including one case in which two smaller agencies were matched to a larger one). Matching accounted for characteristics plausibly related to the TVS outcome: agency type, primary location/borough and program size (measured via a combination of CCP caseload at the time of re-award and award amount). While randomization could not feasibly be stratified by each of these variables, the lead analyst suggested pairs maximizing similarity on these variables. Pairings were finalized with input from other team members knowledgeable about the programs/agencies involved. The lead analyst used a random number generator in Excel to determine agency assignments within pairs, and assignments were communicated as contract conditions in the notifications of awards.

Blinding

Blinding was not feasible for this study. Assignments were transparent to implementing agencies, study team members and interested stakeholders, since contracts are publicly available information.

Data collection, management and analysis

Data collection

As with prior studies of CCP effectiveness,[8 10–12 18] the outcome measure for clients in both study arms will be derived from the NYC HIV surveillance registry ('the Registry'), a population-based data source of electronically reported longitudinal laboratory (VL, CD4) records on all diagnosed NYC PWH.[33 34] Use of the Registry allows near 100% ascertainment of VS for PWH in NYC HIV medical care, regardless of

specific NYC medical provider, and for periods extending before and after program enrolment or discontinuation.

Each client's CCP/CCR enrolment agency and start date are determined from a database of contractually required Ryan White Part A provider reporting to the Health Department, the Electronic System for HIV/AIDS Reporting and Evaluation (eSHARE). These program reporting-based measures are available (non-missing) for all CCP/CCR clients and all implementing agencies. Program data collection forms are located on the NYC Health Department website (https://www1.nyc.gov/site/doh/health/health-topics/aids-hiv-care-coord-tools.page).

Data management and quality assurance

All data for the trial are entered as part of established, legally or contractually required reporting, and are protected according to CDC physical and electronic data security and confidentiality policies.[35] Health Department staff clean and freeze surveillance data sets on a quarterly basis, and conduct matches of program to surveillance data semi-annually, with human review of each near-match by two independent analysts and a separate 'tie-breaker' when the analysts' determinations differ. Details on the deterministic matching algorithm have been previously described.[36] Through the match, participants are assigned a unique record number used in merging surveillance and programmatic data for analytical data sets, which are stripped of all personal identifiers prior to analysis and stored on the most secured drives on the Health Department network. eSHARE data quality is checked by Health Department analysts at the time of each monthly extraction. For purposes of payment, provider agencies also review draft extracts and fill in any missing enrolment and services data monthly.

Statistical analysis for the matched-pairs stepped-wedge trial

Analysis overview and rationale.

We will apply an innovative, fully conditional analysis that, in addition to allowing for arbitrary period effects, allows for arbitrary within-pair site differences. The analysis plan is based on the exact, conditional distribution theory of non-central multiple hypergeometric distributions and their convolutions,[37] which will enable us to estimate and test the effect of the revised intervention as a single parameter defined below. The conventional statistical analysis proposed for cross-sectional stepped-wedge designs (i.e., with independent samples of clients enrolled at each step)[38] assumes a mixed model with random cluster effects and fixed period effects, but this is not appropriate for our matched-pairs stepped-wedge trial. For one, the matching of pairs is under the investigators' control and so should be conditioned on. Second, the generalized linear mixed model has limitations, such as a gratuitous and unverifiable assumption of normal distribution for random effects and poor variance estimation performance in small samples (of clusters), even with robust variance estimation, such that jackknifing must be used. However, the following exact analysis avoids those problems by conditioning out the nuisance parameters.

Analysis approach and assumptions.

As shown in table 3, for each pair of sites, we will produce two 2×3 tables (one table per site in pair), cross-classifying the number of TVS and non-TVS outcomes in Period 0 (with original CCP but no CCR implementation), Period 1 (with CCR only at sites assigned to an early start) and Period 2 (with CCR at all sites). For identification purposes, we refer to 'Site 1' within a matched pair as the site randomized to

switch in Period 1 (early start) and 'Site 2' as the site randomized to switch in Period 2 (delayed start). We begin by assuming the following logistic regression model for the three binomial outcomes: the logit of the probability of TVS for a given site, period and intervention (CCR versus original CCP) equals an intercept representing an arbitrary, pair-specific log odds on TVS for Site 2 in the pair, plus an arbitrary log OR (LOR) for Site 1 versus Site 2 in the pair (allowing for imperfectly matched sites), plus two arbitrary pair-specific LORs for Period 1 and Period 2 effects relative to Period 0, plus one structural LOR of interest, the global intervention effect (non-existent in Period 0, applicable to Site 1 in Period 1, and applicable to both sites in Period 2). The exponent of this last parameter is the target of statistical inference, namely, the OR for TVS versus non-TVS comparing the CCR to the CCP. A key assumption is that any site effects apply in each period and any period effects apply to each site, independent of the intervention effect (i.e., that there are no site-by-intervention or period-by-intervention interactions). This assumption will be tested and the model elaborated if needed. Note that under the key assumption, the constant site and period effects are allowed to vary arbitrarily from one matched pair to the next.

Table 3: Illustration of 2x3 tables cross-classifying TVS and non-TVS outcomes by period.

		Period 0	Period 1	Period 2	Total
	TVS	X_{i10}	X_{i11}	X_{i12}	X_{i1+}
	No TVS	$N_{i10} - X_{i10}$	$N_{i11} - X_{i11}$	$N_{i12} - X_{i12}$	$N_{i1+} - X_{i1+}$
	Total	N_{i10}	N_{i11}	N_{i12}	N_{i1+}
Site 2 in pair *i* (adopts CCR in Period 2)	TVS	X_{i20}	X_{i21}	X_{i22}	X_{i2+}
	No TVS	$N_{i20} - X_{i20}$	$N_{i21} - X_{i21}$	$N_{i22} - X_{i22}$	$N_{i2+} - X_{i2+}$
	Total	N_{i20}	N_{i21}	N_{i22}	N_{i2+}
Pair *i* totals	TVS	X_{i+0}	X_{i+1}	X_{i+2}	X_{i++}
	No TVS	$N_{i+0} - X_{i+0}$	$N_{i+1} - X_{i+1}$	$N_{i+2} - X_{i+2}$	$N_{i++} - X_{i++}$
	Total	N_{i+0}	N_{i+1}	N_{i+2}	N_{i++}

- Light grey cells represent the two 2×3 tables in site pair i. Dark grey cells represent the margins upon which the analysis will condition, whereas white cells represent the margins calculated by summing or subtracting other fixed margins.

Estimating the CCR intervention effect.

Next, by conditioning on the marginal totals within each site (numbers of eligible clients enrolled in each period and total numbers of TVS and non-TVS outcomes for each site), the joint distribution of the numbers of TVS outcomes for Site 1 by period becomes a non-central multiple hypergeometric distribution with only three parameters (the period LORs and the intervention LOR); that is, the conditional distribution does not depend on the nuisance site parameters. By further conditioning on

the sum of TVS outcomes across the two sites in each period, the fully conditional joint distribution depends on only one parameter, the intervention effect; that is, the fully conditional distribution depends neither on the nuisance site effects nor on the nuisance period effects. In fact, the sufficient statistic for the intervention LOR in the fully conditional likelihood function is simply the number of TVS outcomes from Site 1 in Period 1. It is then straightforward to calculate the marginal distribution of this outcome as a function of the intervention effect. Therefore, we will calculate that distribution for each of the 8 matched pairs (including the case of two programs jointly matched to a third) and convolute those distributions to obtain the sampling distribution of the sum of sufficient statistics. Once we obtain the fully conditional sampling distribution of the sufficient statistic as described above, we will report the conditional maximum likelihood estimate of the intervention LOR with an exact, test-based 95% CI. The test of the null hypothesis at the two-tailed 0.05 significance level will be based on the exact two-tailed p value (using the point probability definition),[37] and will form the primary outcome analysis. In sensitivity analyses, we will also report the Wald, Score and Likelihood Ratio test results, which should be close to each other, given client numbers per site per period and the level of TVS from baseline CCP data.

Citations

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