Official title: Flu2Text: Text Message Reminders for 2nd Dose of Influenza Vaccine

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Flu2Text: A Multi-Site Study assessing an Intervention for 2nd Dose of Influenza Vaccine

Overview of the study

This study will assess the impact of text message reminders on the receipt of the second dose of influenza vaccine and will take place in 40-50 practices over two influenza seasons.

This study includes a sample of up to 4,000 parents over the course of two flu seasons (up to approximately 40-250 parents any of 40-50 sites per influenza season). Eligible parents will have a child who received their first vaccine dose and are in need of 2 doses that season. The study will include parents who have a 6-month through 8-year-old child (or a child who is of the age that necessitates 2 doses, should age recommendations change as determined by the CDC) who received their first vaccine dose and is in need of 2 doses that season. Current recommendations require 2 doses for certain children 6 months through 8 years old.

Within each practice site, parents will be randomized to receive either:
1) a series of text message reminders embedded with influenza vaccine health-literacy promoting information, or
2) usual care

- *Season 1 (2017-2018):* usual care alone
- *Season 2 (2018-2019):* usual care plus a text message containing a link to health and parenting information from the American Academy of Pediatrics website

The primary outcome will be receipt of two doses of influenza vaccine by the end of the season (April 30). A secondary outcome will be timeliness of receipt of 2nd dose.

The study will be conducted over the 1st season (September 2017–April 2018) as an effectiveness trial and the 2nd season (July 2018–April 2019) as a replication study to validate the approach and allow refinement based on parent and practice feedback. The intervention targets the parent-child dyad.

Background

Influenza, as evidenced by seasonal epidemics, remains a significant and largely preventable source of morbidity and mortality resulting in an estimated 31 million outpatient visits, 226,000 hospitalizations, and 3,000 to 49,000 deaths annually (depending on the virulence of the circulating strain), along with a high cost burden from direct medical expenses and days lost from work.[1-3] Young children, the focus of this proposal, are at especially high risk for hospitalization and serious influenza complications including pneumonia and neurological outcomes like seizures and encephalopathy. They are also a source of transmission to other high-risk household members.[5-12] However, influenza vaccine coverage is low.[4] Only 58.9% of U.S. children 6 months to 17 years-old receive at least one needed influenza dose annually.[4] Young children <9 years are at particular risk for under vaccination because they require 2 doses at least 4 weeks apart in the first influenza season they are vaccinated, since one dose does not confer adequate influenza protection[12-19]; some previously vaccinated children also require 2 doses in subsequent seasons depending on their previous influenza vaccinations.[12-15] Even among those who need two doses in a given season and who receive the first dose, only 40-60% receive the second dose.[20-22]

Timeliness is also key, as children are not fully protected until two weeks after receiving the second dose;[12, 24, 25] many children do not receive this second dose close to 4 weeks after the first, as recommended.[20] This delay leaves many children unprotected when influenza virus begins circulating.[26] Increasing timely receipt of second doses is also a worthwhile focus as parents (meaning the adult in a parenting role, including guardians) have already "accepted" vaccination as evidenced by their child receiving the first dose.

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Protocol

This proposed study will assess the impact of personalized text message reminders embedded with influenza vaccine health-literacy-promoting information versus usual care on the outcome of receipt of the second dose of influenza vaccine in a given influenza season.

Study Aims:

AIM 1: To compare the effectiveness in increasing receipt of the second dose of influenza vaccine of personalized text message reminders embedded with influenza vaccine health-literacy-promoting information versus usual care in a diverse pediatric population in need of two doses in a given influenza season.

AIM 2: To compare the effectiveness in improving the timeliness of the second dose of influenza vaccine of personalized text message reminders embedded with influenza vaccine health-literacy-promoting information versus usual care in a diverse pediatric population in need of two doses in a given influenza season.

AIM 3: To assess parental and child characteristics that modify text message effectiveness.

Study procedures

Practice inclusion criteria:

- Ability to recruit a minimum of 40 English or Spanish speaking parents per season
- Ability to check the office medical records and/or the city/state immunization information system of the child of the participating parent to confirm dates of first and second influenza vaccination and related visit dates in each season (and ability to provide these dates to the study team)

Practice exclusion criteria:

- Practices that already use or plan to use text message reminders for the second dose of influenza vaccine during the study period

Parent inclusion criteria:

- Parenting adult (or legal guardian) of a child that:
  - is between 6 months through 8 years at the time of enrollment (or a child who is of the age that necessitates 2 doses, should age recommendations change as determined by the CDC)
  - received 1st dose of influenza vaccine within last 7 days (6 days plus date of vaccination)
  - receives care at study site
  - needs 2 doses of influenza vaccine that season as determined by their provider at the study site.
- Ability to communicate in English or Spanish
- Has a cell phone that has text message capabilities

Parent exclusion criteria:

- Parenting adult of a child that:
  - already enrolled in the study in this or the previous season (see Attachments E.2 & I.2)
- Unable to communicate in English or Spanish
- Unable to receive or read text messages on their cell phone

Below we outline the different procedures planned for the study:

Season One: When parents/children come to the practice to receive an influenza vaccine, a member of the care team at the practice site will use the Eligibility Flow Sheet to determine their eligibility for the study. If eligible and parent is interested, the care team member will introduce the study to the parent by providing a parent study information card and a copy of the parent information sheet, available in either English or Spanish. Parents who are potentially interested in the study will be asked to send a text message to the study text message platform. Families will be called to be enrolled. Parental verbal consent and HIPAA authorization will be obtained via phone by study staff.

Season Two: Parents presenting for visits with age-eligible children up to/including the initial flu vaccination visit will receive a study information sheet in either English or Spanish. Providers and practice staff will be asked to approach all eligible parents and provide them with the information sheet. At the visit when the child will receive the first flu shot, a provider or member of practice staff will use the Eligibility Flow Sheet to determine whether the child needs two flu shots this season and whether the child's parent can communicate in either English or Spanish. This recruiting practice staff member will present the Parent Information Sheet to the parent. If the parent is interested and the practice enrolled patients in the 2017-18 flu season, the recruiting practice staff member will assess whether the parent already participated in the study. If there is more than one eligible child in the family, the recruiting practice staff member will enroll the child whose birthday comes next in the calendar year. For example,

if today is October 1 and one child's birthday is January 21 and the next child's birthday is March 4 (regardless of year) then the child with the January 21 birthday should be selected. If the parent is eligible and wishes to participate, verbal consent and HIPAA authorization will be obtained by an HST-certified provider or practice staff member (recruiting practice staff member) at the study practice sites.

Parent randomization

Randomization will occur with a 1:1 allocation ratio stratified by:

- clinical site (such that each site will have a balance of intervention and usual care plus participants)
- child's age group (6-23 months vs. 2-8 years)
- parental language (English versus Spanish preference)

To ensure allocation concealment (a technique used to prevent selection bias), the CHOP/Penn statistician will prepare for each site a separate randomization list stratified by age and language, using randomly permuted blocks with varying block sizes.

If the parent is assigned to usual care, they will receive the existing influenza vaccination protocol for any given practice. This may include other forms of influenza vaccine reminders. In season 2, caregivers randomized to usual care will be sent a message upon enrollment containing a link to health and parenting information from the American Academy of Pediatrics website. If a parent is assigned to the intervention arm, we will follow the protocol under *Study Intervention: Text Messages.*

Study Intervention: Text Messages
Messages will be sent in English or Spanish based on parent preference.
Using date of initial vaccine as day 0, text messages will be sent to all parents randomized to the intervention on the following days:

- Day 14: notifying parents that their child is in need of a second flu shot.
- Day 21: educational text messages, with interactivity, through which parents can select to receive more information via text message.
- Day 25: letting parents know when and where they will need to go to receive the second shot
- Day 28 (day vaccine is due): it is now time to take [child] to be vaccinated (2nd flu shot).
- Day 42 (2 weeks after it is due): another interactive message will assess potential vaccine barriers and offer selected responses.

Texts will stop after day 42. We will not be able to know from the practices in time to stop messages after a child was vaccinated. However, as the shot is not due until day 28, it would likely only be the day 42 message that could come after the child was vaccinated. That message has been worded to first assess whether the child received the vaccine.

Dates of influenza vaccinations and related visit dates: Dates of influenza vaccinations and related visit dates will be collected from the practices. The part of the Patient Enrollment/Outcomes Forms that stays with the site will have child's first and last name and date of birth. The site will use this to identify the medical record, extract relevant influenza vaccination dates and related visit dates and transfer this information to the research team. Practices will do this by using their medical records and/or by checking their city or state immunization registry should the practice have no record of receipt of subsequent influenza doses for the current season.

Statistical Analysis Plan (SAP) – Flu2Text - v1.6

Date of final SAP: September 12, 2019

This plan, based on the original proposal and the IRB protocol, will guide analyses. It follows the aims outlined in the proposal. In keeping with recent guidance of the American Statistical Association, we will avoid statements about "statistical significance". When reported, p-values will be continuous, unless they are below 0.001, when we shall use the notation "$p<0.001$", in keeping with general guidance on very small p-values. We shall report p-values with 2 decimal places if they are larger than 0.10 and to 3 decimal places otherwise. Point estimates and confidence bounds will be the primary means of reporting results and their precision. Primary analyses are reported below where indicated. Software tools are also listed, but are subject to modification if they fail to converge or produce results.

For overall guidance, we will follow those from New England Journal of Medicine (Last accessed, Sep 11, 2019).

We shall date this SAP upon agreement and completion and then date all amendments.

1.0 Data management

We shall examine each covariate to identify ambiguities and to categorize when appropriate to avoid zero and small categories. All refinement of covariates will occur prior to any examination of outcomes.

Cross classifying X's will determine which X's are correlated, aliased, how many levels can be collapsed. The goal will be to find a set of covariates for use in describing the sample and comparing the two treatment groups for balance. In these analyses, we should not be looking at outcome.

2.0 Analysis *(A) Primary analysis: As randomized (Aims 1 and 2).*

AIM 1: To compare the effectiveness in increasing receipt of the second dose of influenza vaccine of personalized text message reminders with embedded influenza vaccine health-literacy-promoting information versus usual care in a diverse pediatric population in need of two doses in a given influenza season.

AIM 2: To compare the effectiveness in improving the timeliness of the second dose of influenza vaccine of personalized text message reminders with embedded influenza vaccine health-literacy-promoting information versus usual care in a diverse pediatric population in need of two doses in a given influenza season.

2.0.1 Analyses will proceed separately by season

Seasons 1 and 2 will be analyzed separately.

Secondary analysis will combine seasons, adjusting for season as a stratifying factor. Site will be considered to be a separate stratum by season.

2.1 Analysis – binary outcomes – primary analysis and outcome

Outcome = Receipt of the second dose of influenza vaccine, a binary outcome.
By April 30, the end of the season - primary
By Day 42 from the day of first dose - secondary

Formal question to be answered: "If a group of children were alternatively assigned to the two treatment arms, what would be differences in completion of influenza vaccines by the end of the season, defined as April 30th of each season?"

The alternative and secondary endpoint will evaluate receipt of the second dose as of day 42 from the date of the child's first dose.

Randomization, if successful, should lead to exchangeability of two groups and permits estimation of the treatment differences (as the control group should be the same as the intervention group).

Preliminary analysis of time from the first dose to time of randomization showed no difference between intervention and control groups, and reflects successful randomization. This analysis was conducted as part of assessing balance and without regard to outcomes.

Primary analyses will proceed where possible with assumption-free methods. Dropout was negligible and so adjustment for dropout was not needed nor specified in the final SAP.

2.1.1 Testing for balance from randomization based on patient-level covariates

The initial check will be whether randomization produced balance of the sites and covariates. For this check, we will fit a model:

Outcome is treatment assignment. Logistic regression – with all covariates included.

1. Check that overall likelihood ratio statistic is not significant.
2. Suggests overall balance consistent with successful randomization.

Balance check covariates:

- time from 1st (initial) dose to randomization
- child age
- child gender
- text language
- child health insurance

2.1.2 Unadjusted association of treatment assignment and outcomes

After checking for balance across patient characteristics, we shall estimate treatment-outcome associations assuming binary outcomes

2.1.2.1 Relative risks

Stratified (by site and language) Mantel Haensel

Estimates = RR and confidence interval

Make a new variable that is the combination of site and language = l_site

Stata: cs outcome treatment, by(l_site)

This is a "fixed effects" analysis and does not consider the effect on variance of variation across sites in the effect of treatment (See section 2.4).

2.1.2.2 Binary outcomes – risk differences

Risk differences are important measures and should be reported along with relative risks. But standard packages do not report risk differences using Mantel Haenszel approaches. There are two alternatives that might be indicated.

Alternative #1. Newcombe

SAS: Alternative – Mantel Haenzsel methods for risk difference with Newcombe confidence bounds.

Let "strata" be the combination of site and language.

```
PROC FREQ;
Tables strata*treatment*outcome/riskdiff method=newcombe;
Run;
```

Alternative #2. Bohning (Biometrics 2000) - confirmatory

Bohning proposed, and we have programmed in Stata, a Mantel Haenszel approach for estimating risk differences. We propose to use this as our primary approach and then to use Newcombe as a check on sensitivity. Both methods might be helpful because risk differences (stratified) are not as well-accepted as methods for stratified relative risk. This will be a secondary analysis only for purposes of confirmation.

Binary outcomes are (as noted above): Second dose status as of April 30 (primary), and as of day 42 from child's date of first dose (secondary).

2.1.3 Analysis with covariates (if check on balance fails)

2.1.3.1 Conditional logit models (likely not applicable owing to randomization)

Conditional logistic regression model, adjusted for covariates, stratified by site.

Stata: clogit outcome treatment covariates, group(site)

Compare with the model (covariate unadjusted) such as Mantel Haenszel approaches.

Stata: clogit outcome treatment, group(site)

Do the estimates of the effect of treatment differ between these two models? If yes, then some chance imbalance in covariates across treatment groups is imparting some bias in the unadjusted estimates.

2.2. Continuous outcomes (if any) – not applicable

We have none. This section is not developed.

2.3 Secondary analysis: Time to event (Aim 2)

As a secondary outcome, and to confirm that statistical significance from our primary analysis applies equally to time to event data, we will use stratified (by practice site) time-to-event analysis for receipt of vaccine.

Our goal will be to use, where possible, assumption free methods and avoid parametric approaches, and at the same time to present results in a format that can be interpreted easily to a clinical audience. For these reasons, we are deliberately avoiding traditional approaches such as Cox regression and common metrics such as hazard ratios.

This section covers two separate topics:

> First, in keeping with our goal of using assumption-free, randomization-test based methods, we shall apply this approach to time-to-event analyses.
>
> Second, we shall estimate restricted mean survival times to arrive at more meaningful estimate of time to event and to avoid "hazard ratios"

2.3.1 Time zero

Time zero for all time to event analyses is the date of child's initial vaccine dose.

2.3.2 Descriptive Kaplan-Meier (KM) curves of time from 1st to 2nd dose

Non parametric Kaplan-Meier curves:

> Stata: "sts graph"

These will be done with censoring date April 30 (primary) and day 42 (secondary). Both analyses will be reported and plotted

We will use inverted KM curves. This graphical approach will be our primary analysis. Log rank tests will generate p-values if proportional hazards assumption met. Stratification will be by clinic site.

2.3.3 Stratified randomization test based estimates - confirmatory

Randomization-based estimates are now available for stratified data in Stata with the program strbee (White 2002). Later versions support stratification. These are iterative, grid search based estimates for inverting the test statistic.

> In Stata: Must download latest version using "net search strbee"

The key is the use of "strata()" command below. Then the syntax is:

Stset timevar, failure(failure_indicator)

Strbee treat_var, test(logrank) endstudy(time_to_end_study_var) strata(site) adjvars(covariates)

2.3.4 Risk difference (of completion of vaccine series) as of a given time

The purpose of this analysis is to re-express the results of Kaplan Meier survival estimates to generate more interpretable results. It is therefore an alternative method to express the results and will not be considered as a multiple test in need of adjusting confidence intervals. This analysis is not separate from the Kaplan Meier analysis. Rather it only quantifies the values of the two curves (y) at a given value of time (e.g. 42 days). This is therefore, just a re-expression of the Kaplan Meier plot.

Use of pseudo-observation approach with syntax:

Stpsurv, at(time1) failure after(time0),

Where time(1) can be as of day 42, 60, and 90.

As April 30 does not account for different days of follow up per child, it will not be possible to use that date for analysis. Programming details appear in Stata program "stpm2" (Lambert, Andersson, Royston).

Syntax is (approximately):

standsurv, at1(treatment 0) at2(treatment 1) timevar(timevar) ci contrast(difference)

See stpm2 syntax for "standsurv"

"ci" refers to cumulative incidence

"timevar" needs to take on the value 42, 60 and 90

2.3.5 Restricted mean survival curves (RMST)

RMST will not be a primary analysis, and we will not consider it to be a separate look at the data. Rather, it is another method of reporting the data, and we will not adjust confidence bounds for multiple comparisons.

We will implement restricted mean survival time analysis to compare intervention versus usual care groups (if needed, after adjusting for covariates that are not balanced

between groups) and to arrive at meaningful estimates that do not require proportional hazards assumptions.

We have moved beyond hazard ratios because of the assumptions underlying Cox models and the shortcoming of interpretations (Hernan 2010). If we set a truncation time (Day 42), then RMST has the interpretation "if we follow children for 42 days, they will receive the second vaccine on average by day X" (Royston 2011, 2013). Estimation of between group differences are also possible. The more theoretical interpretation is the area under the survivor function until the time of truncation.

Preiminary analysis of available time per child (analysis blinded to outcome and to the treatment assignment) showed that between 84% and 90% (depending on season) of children has observation windows that extended to day 90 from date of first dose.

2.3.5.1 RMST

Stata: strmst2:

RMST and curves are estimable using strmst2 (Cronin 2016) in Stata

Will perform conventional RMST analysis:

Requires “stset” as preliminary command.

Strmst2 treat, tau(50) (will not allow factors), where "tau" is the largest time of observation and should be the minimum (by group) of the maximum follow up time (within group).

Observation time starts at the time of the first dose of vaccine and ends on April 30, of the season year or when the child received the second does, whichever was earlier.

For this study, we pre-specify several values of tau:

(i) 42 – the number of days within which children should receive the second dose
(ii) 60 days
(iii) 90 days

Adjustment for covariates using strmst2pw

Robust confidence intervals.

This approach has no support for robust confidence intervals (or for strata). For that reason, we will check all confidence bounds by using bootstrap percentile methods, with 999 resamples at the site level (code will be developed for Stata).

Note: Alternative RMST code available from Royston (2015) using Stata’s code strmst. This will be a backup in the event that Cronin’s code fails.

2.4 Tertiary analysis: Variation across practice sites - descriptive

We anticipate that the effect of the intervention could vary across practice sites.

2.4.1 Binary outcomes

2.4.1.1 Mixed effects models

To assess this potential for variation in effect across the intervention sites, we will consider generalized linear mixed effects models (logistic regression with random intercepts and slopes) to mimic the analysis that would occur in a meta-analysis in which variation across sites is expected. The advantage of this approach is that once the random slopes (treatment effects estimating the departure of each site from average) are estimated, we can identify the sites that have either high or low treatment effects. Individual site estimates are shrunk toward the overall average in these methods to avoid problems of unstable site-specific estimates and to reduce the problem of multiple comparisons. This method will, however, allow us to identify the sites with the greatest and least improvements. Once identified, we will attempt to characterize these sites and contact them to discover the possible barriers to improvement.

If mixed effects models reveal no varation of intervention effect across sites, when that result will reported and this analysis will stop.

Generalized linear mixed effects models. Stata melogit for binary outcomes:

Random intercept (and slopes) for each site (assuming correlated intercept/slope)

Overall test for variation across sites in treatment effect

Likelihood ratio test of random slopes

2.4.2 Time to event outcomes – variation across sites

We will use the same approach for time to vaccination, with mixed effects models and letting site be a random effect. In other words, we allow estimated time to vaccination vary by site, and test whether this variation is significant.

Statistical significance of the random site effect can be testing using likelihood ratio statistics.

Stata: mestreg –

```
mestreg treat covariates || site:, distribution(weibull) int(12)

predict resite, reffects
```

In this example, the variable "resite" will contain the value for the "prediction" at the site level. The prediction will then represent the site-level time to event, and by ordering the sites by this value, we can determine which sites fared best and which fared worst.

R: coxme

Alternative but similar approaches are now in R (Therneau 2018) for the Cox model

3.0 AIM 3: To assess parental and child characteristics that modify text message effectiveness

The goal for this Aim is to identify subgroups for which the intervention was either particularly effective or not effective. All subgroups should be pre-specified (see candidates below). They should also be few, owing to issues of multiple comparisons. For that reason, all confidence bounds of subgroup estimates will be adjusted so that bounds correspond to Bonferroni corrections for multiple contrasts. This aim is exploratory.

3.0.1 Candidate effect modifiers

The following factors represent the original candidate effect modifiers.

3.0.1.1 Available for all children

- child age-group (6-23 months; 2-8 years)
- child gender (male; female)
- child health insurance (public/unisured; commercial (including Tricare)). This variable is used as a partial indicator of socioeconomic status.
- seasonality of the initial dose (early influenza season, mid-season, late season)

3.0.1.2 Available for all caregivers

- text language (English; Spanish)

3.0.1.2 Available for all practice sites

- appoitment scheduling for the 2nd dose (walk-in; appointment)
- primary practice setting/urbanicity (urban, inner city; urban, not inner city; suburban; rural). Practice setting is self-reported and the categories align with the Periodic Survey from the American Academy of Pediatrics.

3.0.1.3 Available for only questionnaire respondents

Caregiver:

- age

- highest education level
- relationship to a child
- receipt of previous text message reminders from their practice site/doctor
- type of text message plan
- text messaging frequency
- overall childhood vaccine hesitancy
- flu shot safety
- perceived risk of getting sick from the flu

child:

- reported health status
- race/ethnicity (including sub-group)

The first challenge is to try to identify potential subgroups based on groups of these individual factors without making the error of estimating each candidate factor one by one and then looking for "interaction" of treatment by factor.

3.0.2 Effect modification on the additive scale

We define effect modification on the additive scale for the effects of treatment on outcome. For binary outcomes, effect modification therefore means that the effect of treatment is in terms of "percentage points" of improvement, and effect modification is present if improvement (in terms of percentage points) from the intervention differs by the effect modifier grouping.

3.0.3 Latent class analysis of patient-level factors - exploratory analysis

Latent class analysis can reduce many patient level factors into a single dimension factor. (Lanza 2013). With our candidate factors distilled into a categorical latent class, we propose to simplify the process of identifying and reporting potential effect modification. These analyses will be exploratory

3.1 Subgroup analyses – binary outcomes – primary analysis

We will pre-specify subgroups of interest based on combinations of patient characteristics. Risk differences, rather than relative risks, will be the scale on which to estimate treatment*subgroup interactions, so that final results we can report in terms of percentage points of improvement.

3.1.1 Estimating within site effects of subgroups

The within-site effect modification estimate represents the difference in treatment effects across levels of the effect modifier contrasted within (rather than across) sites. For this estimate we shall first use a linear fixed effects model, as implemented in Stata command "xtreg,fe", assuming that the outcome will lie in the probability range of 0.2 and 0.8.

This approach will be a first estimate to be followed by the decomposition approach in section 3.1.2.

3.1.2 Parametric subgroup analysis – decomposing the within and across site effects

We assume that absolute rates (risks) of second vaccine will not lie at the ends of the interval [0,1]. If that is the case, then we can estimate risk differences with subgroups and then across subgroups in the following 3-step process.

Step 1: Using a generalized linear effects, create a site-level variable that equals the mean rate of the group at the site. If at one site, for example, 20% of the children have a chronic medical condition, then create a factor =0.2 for that site (called group_bar).

Step 2: Specify a generalized linear model with the following covariates where treatment and group are 0/1 factors:

Treatment + group + treatment*group + group_bar + treatment*group_bar + covariates.

This model will decompose the within-site effect of treatment by group and the across-site effect of treatment by group.

3.2 Subgroup analysis – time-to-event – secondary

The goal is to identify subgroups of patients who responded well (or not at all) to the intervention in terms accelerating the time to completing of the vaccination series. Contrasts between groups will be estimated and reported as

Restricted mean survival time analyses can be done with interactions (treatment*subgroup).

Effect modification will be estimated on the difference scale.

Using pseudo-observation approach:

Stata: glm pseudo treat##subgroup, vce(cluster site)

Results can be standardized for covariates (see above).

3.2.2 Permutation-test based confirmatory subgroup analysis - confirmatory

The STEPP package in R (in theory) can implement permutation-based analyses for binary outcomes (as well as count, continuous and survival) (Yip 2016). This approach will be confirmatory as well as exploratory, and as time permits, and will be applied to the case of multiple subgroups defined in terms of latent classes, and will be

used for the primary outcome (binary) and for the time to event estimate. If the approach runs, we shall report all results, as confirmatory.

[Tested using stepp data. Remains for testing using actual study data.]

4.0 Season specific estimation

There is interest in estimating differences by season, and for that reason we will estimate treatment effects separately by season as well as combined overall.

Proposal: Consider each season*site combination to be a stratum and do the analysis heavily stratified. If there is a need to consider differences by season, then treat season as a separate, site-level effect modifier.

5.0 Amendments

We have made the following amendments on the dates notes and for the reasons noted.

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