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ADHD Enhanced Portal Statistical Analysis Plan

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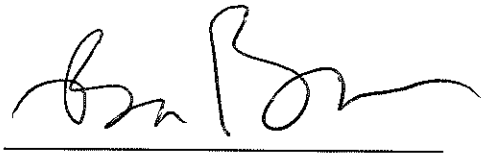

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The results of the ADHD Enhanced Portal Pilot study Aim 3 will be assessed as described in this document. This statistical analysis plan begins with an overview of the key components of the study including its design, objectives, and outcome measures. This is followed by a detailed description of the statistical analyses that will be utilized to address Aim 3 study hypotheses.

1. Overview of study: This study is a multi-practice, cluster randomized trial to evaluate the effectiveness of an Enhanced ADHD portal. Practices that agree to participate in the study were randomized 1:1 to receive either the intervention (enhanced ADHD portal) or the control group (standard portal) prior to subject enrollment. We used a covariate-constrained randomization procedure to ensure that the intervention and control practices were balanced with respect to: 1) number of health care providers and 2) average percentage of Medicaid patients (Ivers et al. 2012). We planned to enroll a total of 80 children newly diagnosed with ADHD from 8 practices in this trial (40 from the intervention practices and 40 from the control practices).

1.1 Study Objective: Evaluate the general effectiveness of the intervention (e.g. enhanced ADHD portal), compared to control (e.g. standard portal), on medication continuity as measured by prescription records and other more proximal outcomes during the first six months of treatment.

> Working hypothesis 1: compared to the control group, the intervention group will have greater medication continuity as measured by number of days covered with medicine.
>
> Working hypothesis 2: compared to the control group, the intervention group will have greater proportion with parent entered data to track response to treatment.

1.2 Outcome measures

Primary

- Medication continuity as measured by number of days covered with medicine within 6 months of medication start.
    - Number of days covered with medicine is calculated from audit of prescriptions written during the first 6 months of treatment.

Secondary

- Proportion with parent entered data to track response to treatment
    - Entered data is defined by completion of at least one parent-completed Vanderbilt (VADPRS) between medication start to 6 months post medication start
- Total number of measures completed by parents to track child response to treatment from date of medication start to 6 months post medication start
    - Measures completed are defined by completion of the Vanderbilt (VADPRS)
- Number of family portal logins from date of registration to 6 months post mediation start.

1.3 Intervention Fidelity measures

Intervention group only

- Proportion of parents who completed the Shared Decision-Making component
- Proportion of parents who selected an outcome measure (defined as set a behavior to be tracked)

- Proportion of parents who entered monitoring data (defined as filled in behavior rating data)
- Proportion of parents who received text messages
- Proportion of parents who used the social forum (starting 3/6/16)

1.4 Schedule of visits and time points of interest

- Registration on the portal (usually before consent)
- Consent date
- Baseline survey (baseline, after consent, usually a few days after)
- Medication start (varies by subject)
- 6 months post medication start, 6-month survey (completion)

1.5 Data Management

CCHMC CRC will guide data management for this project as described in the study protocol.

1.6 Interim Safety Analyses

No interim analyses are planned for this study.

2. Statistical Reports

2.1 Report Generation

2.1.1 Deviations from Statistical Plan

The final statistical reports will describe and justify any deviations from the original statistical plan described herein.

2.1.2 Software

The statistical reports will be prepared using SAS 9.4 and R 3.3 under Microsoft Windows operating system.

2.2 Analysis Populations

2.2.1 Screen Failures

Subjects who are recruited but do not give written consent are considered screen failures. Subjects who give informed written consent but are determined ineligible post-consent are considered screen failures. Screen failures will not be included in the analysis.

2.2.2 Intent-to-Treat (ITT) Population

The ITT population is defined as all subjects who consented and started ADHD medication.

2.2.3 Completion

Patient will be considered to have completed the study once the patient completes the 6-month post medication survey or study end date on 9/24/17.

2.2.4 Outliers

The data management and statistical analysis teams will identify subjects having data values that appear to be potential outliers. These values will be sent to the research coordinators for verification. Clear

identification of a value as an outlier will be based on medical judgment as well as on statistical grounds. In the event that outlier values are identified, any analysis using the actual values will be followed by an analysis that reduces the outlier effect.

2.2.5 Missing data

We will complete chart audits of prescriptions written to calculate our primary outcome for all study participants unless consent is withdrawn. Our approach for handling missing data will be to first assess consent withdrawal rates and evaluate whether or not the rates are very different between the two arms of the trial. If the rates/reasons are similar, we will perform the analysis assuming *Missing Completely at Random (MCAR)*, i.e., the propensity for a data point to be missing is completely random such that there is no relationship between whether a data point is missing and any values in the data set, missing or observed (missing data are a random subset of the data). If consent withdrawal rates are very different between the two arms of a trial, then our results will be limited by concerns about potential bias.

For secondary outcomes, missing outcome data could occur for several reasons such as item nonresponse, lost to follow-up, and data collection errors. Secondary outcomes are supportive and exploratory in nature, thus we will not impute missing secondary outcomes. Results of secondary outcomes will be limited by potential bias due to missing data.

2.2.6 Protocol Violations/Withdrawals

If a study participant is to be excluded/dropped from the study database and/or analysis, the PIs/coordinators will provide to the statistical analysis team the following: 1) the specific reason for dropout (e.g., withdrawal, protocol violation), in as much detail as possible; 2) who decided that the participant would be excluded; and 3) whether the exclusion involves some or all types of participation.

2.3 Statistical Report Contents

The following section outlines the contents of the final statistical analysis. For all analyses, baseline is defined as the measurement collected during the baseline survey. Subjects who are enrolled in the study and are eligible will be analyzed in the groups to which they were allocated regardless of actual intervention received.

2.3.1 Description of study population

Sample size:
The total number of subjects who are consented/registered and withdrawn will be given. A summary of subjects who were withdrawn will be provided.

Demographics and Clinical Characteristics, Patient and Parent:
Demographic and clinical characteristics as measured at baseline will be summarized by trial arm. Variables to be summarized are: parent age, parent race and ethnicity, relationship to child, parent sex, parent marital status, parent education, technology use, parent numeracy score, child sex, child age, child race and ethnicity, child insurance. Variables will be summarized using descriptive statistics appropriate for each type of data item.
Baseline characteristics with large differences between groups will be included in analyses evaluating the effectiveness of the intervention.

Practice characteristics:
Practice characteristics measured prior to randomization assignment (start of study) including physician sex, physician race and ethnicity, physician age, years at practice, number of ADHD subjects seen per week will be summarized by trial arm. Variables will be summarized using descriptive statistics appropriate for each type of data item.

2.3.2 Primary outcome analysis

Primary outcome: Medication continuity as measured by number of days covered with medicine within 6 months of medication start.

- Number of days covered with medicine is calculated from audit of prescriptions written during the first 6 months of medication treatment.

For the primary outcome, the dependent variable will be a count of the number of days covered with medicine within 6 months of ADHD medication start date. Differences between intervention and control groups on this outcome will be evaluated using a generalized linear model assuming a Poisson distribution with a log link function. The number of days from start of medication to end of study will be included in the model as an offset. Other potential covariates (e.g. baseline characteristics of child age, and race with large differences between groups) will be included in a secondary analysis model evaluating the effectiveness of the intervention.

2.3.3 Secondary outcome analyses

- Proportion with parent entered data to track response to treatment

The dependent variable will be the proportion with parent entered data to track response to treatment as any Vanderbilts completed by the parent from date of medication start to 6 months post ADHD medication start date. Differences between intervention and control groups on this outcome will be evaluated using a logistic regression model. Potential covariates (e.g. baseline characteristics of age, race, with large differences between groups) will be included in a secondary analysis model evaluating the effectiveness of the intervention.

- Total number of measures completed by parents to track child response to treatment from date of medication start to 6 months post medication start
    - Measures completed are defined by completion of the Vanderbilt (VADPRS)

The dependent variable will be a count of the number of Vanderbilts completed by the parent from date of medication start to 6 months post ADHD medication start date. Differences between intervention and control groups on this outcome will be evaluated using a generalized linear model assuming a Poisson distribution with a log link function. The number of days from start of medication to end of study, 6 months post medication will be included in the model as an offset. Other potential covariates (e.g. baseline characteristics of age, race, with large differences between groups) will be included in a secondary analysis model evaluating the effectiveness of the intervention.

- Number of parent portal logins from registration to 6 months post mediation start

The dependent variable will be a count of the number of portal logins from date of study registration to 6 months post ADHD medication start date. Differences between intervention and control groups on this outcome will be evaluated using a generalized linear model assuming a Poisson distribution with a log link function. The number of days from portal registration to end of study, 6 months post medication will be included in the model as an offset. Other potential covariates (e.g. baseline characteristics of age, race, with large differences between groups) will be included in a secondary analysis model evaluating the effectiveness of the intervention.

2.3.4 Intervention Fidelity measures

Intervention group only

The following will be summarized as count and percentage:

- Proportion of parents who completed the Shared Decision-Making component
- Proportion of parents who selected an outcome measure (defined as set a behavior to be tracked)
- Proportion of parents who entered monitoring data (defined as filled in behavior rating data)
- Proportion of parents who received text messages
- Proportion of parents who used the social forum (starting 3/6/16)

Associations between parent characteristics and intervention fidelity measures noted above will be evaluated using logistic regression models. Separate models will be utilized for each of the 5 fidelity measures listed above. The following variables will be included as independent variables in the logistic regression models:

- Parent Technology use
    - Measured at baseline and defined by use an app to track or manage health (yes/no)
- Primary Caregiver Parent Education
    - 3 levels: HS or less, some college (2 yr or tech), college grad or above
- Parent Numeracy
    - The Subject Numeracy scale measured at baseline
    - Continuous measure

Associations between the 5 intervention measures listed above and medication continuity (primary outcome) measure will be evaluated using the same approach described under the primary outcome analysis. Separate models will be utilized for each of the 5 fidelity measures listed above.