STATISTICAL ANALYSIS PLAN

CHANGING THE DEFAULT FOR TOBACCO TREATMENT

ClinicalTrials.gov Identifier: NCT02721082

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Data Management

Data management will follow procedures developed for EQUIP. UKanQuit service data, and survey data collected by research assistants, will be directly entered via tablet into REDCap. Project Director Mussulman will coordinate data retrieval from the EHR. Data manager Mr. Nazir will conduct initial data cleaning, identifying and tagging any crossovers, conversion into proper format for data analysis, and recoding using standard operating procedures. All data will be imported into SAS for study analyses. Cleaning and management routines (e.g. conversion of birth dates to ages, logical checks for continuous variables, compliance with skip patterns, missing data codes) will be conducted using SAS.

Data Analysis: Overview of Hypotheses and Analyses

The overall study design is a posttest only design with random assignment to groups. We will conduct process, outcome, mediation, and cost analyses. Prior to initiating outcome analyses of quantitative data, we will compare baseline data across groups to evaluate whether random allocation achieved equivalent groups. Bayesian analysis (see *Statistical Model*, below) will answer our main outcome. After verifying adequate SEM fit to the data, i.e., that CFI >.9 and RMSEA < .8, we will use SEM to perform classic mediation analysis using the strategy outlined by Baron & Kenney[1]. When conducting the final analysis we will exclude the following: participants who refused consent, patients who died or are incarcerated. We will test whether there are any systematic differences between the enrolled and non-enrolled population by comparing the demographic and tobacco use patterns of all non-enrolled participants (unable to reach, deceased, incarcerated, refused consent) to those who enrolled (consented) at baseline. This comparison will strengthen considerably the scientific merit of the study by enabling reviewers and readers to judge how representative our study population was to all hospitalized smokers treated.

Study hypotheses, measures, and analytic strategy

Purpose	Variables	Analytic Strategy
Hypothesis 1: Compared to **OPT IN**, significantly more in **OPT OUT** will participate in counseling, use cessation medications, and be abstinent from smoking	Abstinence: Treatment condition and 1-month 7-day point prev. abstinence	Bayesian analysis
	Counseling: Treatment condition and total counseling time by 1 month	T-test
	Medication: Treatment condition and number of days of medication use	T-test
Hypothesis 2: Significantly more smokers in **OPT OUT** will be abstinent from smoking, and mediation analyses will partially or fully explain the effects.	Treatment condition and 6-month and -7-day point prev. abstinence -Default variables -Counseling/medication use	Structural equation modeling with a logistic outcome
Hypothesis 3: **OPT OUT** will be more costly but also more effective than **OPT IN**	Treatment condition and 1-month -7-day point prev. abstinence -Variable costs	Incremental cost/quit

Data Analysis: Bayesian Study Design, Outcome Analyses, and Cost Effectiveness

We will perform a prospective randomized comparative effectiveness *Bayesian adaptive design study*.[2] This approach is a highly efficient and ethical strategy for comparative effectiveness clinical trials design, because it allocates more patients to effective treatments and can answer the research question earlier than conventional designs.[3] In Bayesian adaptive designs, one primary endpoint is used to drive the adaptive randomization. This endpoint is compared across study groups periodically, and more patients are randomized to the stronger arm, until a predetermined probability that one arm has “maximum utility” is reached, which signals the end of the comparative trial. Our endpoint is the percentage of patients who quit smoking at 1-month (4 weeks) post-study randomization. We will perform our first planned interim analyses when we have randomized 400 patients. Based on the 400 randomized patients, the first interim analysis final set will be sub-selected via patients consenting to

be enrolled or patient unable to reach for the 1-month survey, and patients with 1-month survey window closed. The arm that appears to be performing the best will get more participants allocated to it in the subsequent randomization period. A new adaptive randomization structure will be updated every 13 weeks, using up-to-date outcome data, until a) trial meets early success or b) randomize all 1,000 participants. All outcome analyses will use an intent-to-treat approach, in which all participants will be included in the group to which they were originally assigned.

Virtual participant response. In accordance with guidelines for adaptive design power analyses[2], we assumed several virtual (or "pretend") responses to determine the power, sample size and time (duration) needed for our study. We created several scenarios for quit rates using three assumptions. One virtual response is the 'expected' quit rates, another is 'small but unlikely' quit rates, and the third is 'no differences' in quit rates.

Accrual (enrollment) patterns. Accrual patterns refer to how rapidly we enroll patients in the trial. These are important to Bayesian adaptive designs for determining the length of the trial. Based on accrual patterns for EQUIP and other hospital studies conducted by Drs. Richter and Ellerbeck, we assume that the accrual patterns will follow a Poisson distribution with an average of 6.7 patients per week.

Virtual response patterns for quit rate endpoint

	OPT IN	OPT OUT	
		Efficacy	
No differences	15.7%	15.7%	Both have equal quit rates
Small but unlikely	15.7%	20.0%	Opt-Out is moderately better
Expected	15.7%	25.2%	Opt-Out is better at expected differences

Statistical model. For this study the primary endpoint is modeled $S_{Qj}|n_j \sim \text{Bino}(n_j, \theta^Q_j)$ quitting. In addition, we provide "weakly informative" priors, $\text{logit}(\theta^Q_j) \sim N(0,100^2)$. Using the endpoint data and the prior probabilities, we then use Markov Chain Monte Carlo computations to obtain the Bayesian posterior distributions for the endpoint (i.e., quitting.) We will stop the randomizing into the comparative trial if the probability of a study arm having best utility is greater than 0.9925 at both 1-month AND 6-months. The arm (or drug) having the maximum quit rate is $M_T=\max(\theta^Q_1, \theta^Q_2)$. The stopping rule is mathematically $P(\theta^Q_1 > \theta^Q_2) > .9925$ or $P(\theta^Q_1 < \theta^Q_2) > .9925$), this would take place both at 1-month AND 6-month endpoints. If a best arm is not identified after 500 patients randomized, this procedure and accrual will continue until a best arm is identified or we randomize all 1000 patients. Should we reach our stopping rule before 1,000 patients randomized, we will continue to recruit patients, but we will stop randomization and recruit the remaining patients into the more effective study arm. We will do so because this is the first trial to experimentally test the impact of changing a treatment default. We believe it is important to maximize our cases to enable us to conduct mediation analyses that will determine the mechanisms that underlie the impact of treatment defaults.

Adaptive Randomization: allocation. After the best utility probability is evaluated the next round of patients are randomized using a formula, which is $V^*_j=\text{sqrt}(P(\theta^Q_j > \theta^Q_{j'})\text{Var}(\theta^Q_j)/(n_j+1))$ and θ^Q_j and $\theta^Q_{j'}$ are the utility parameter (i.e. smoking quitting rate parameter) of the two arms at 1-month only, that takes advantage of the information gained from our analyses up to that point. The newly enrolled patient allocated to the j^{th} arm is proportional to $V^*_j=\text{sqrt}(P(\theta^Q_j > \theta^Q_{j'})\text{Var}(\theta^Q_i)/(n_{jT}+1))$. This type of allocation tends to have more desirable properties then simply using $\Pr(M_{jT}= \theta^Q_1)$. In other words, using this approach will allow us to assign more patients to the most promising arm, and fewer patients to the least. Regardless of when the probability cutpoint is reached, we will confirm this finding with a subsequent analysis and evaluation (>.99), which can be at 1-month OR 6-month endpoints, after all data from patients are obtained, as some will still be actively in the study when the early success criterion is identified.

Power, sample size, and trial duration. We performed three sets of trial simulations based on the various combinations of quit rates endpoints for both 1-month and 6-months. Each set involved many trial simulations that identified power (the probability of success) in two scenarios—one for early success (i.e., being able to stop randomization early) and one for late success (i.e., upon randomizing all 1000 patients). While two of these combinations are very unlikely to occur, we included all scenarios. First, under the 'expected' quit rates at 1-month and 'expected' at 6-months, we estimated (identified) that 75% of the simulated trials had early success, 24% late success, and only 1% had incomplete results. Thus this scenario had 99% power. The average sample size of this trial scenario was 789 patients with more than half (546) in the better OPT-OUT arm. The average length of these simulated trials was 145 weeks. Second**,** if there is 'expected' quit rates at 1-month and 'small but unlikely' quit rates at 6-months, we estimated (identified) that 23% of the simulated trials had early success, 68% had late success, and 9% had incomplete results. This trial scenario had 91% power and the sample size

of this trial scenario was on average 947 with more than half (696) in the better OPT-OUT arm. The average length of this trial scenario was 167 weeks. Third, we examined the scenario that serves as our null hypothesis (no differences) at both 1-month and 6-months. In this scenario there are no differences in quit rates among the arms. The extent to which this scenario is "successful" actually reflects our Type I error rate. For this scenario, we estimated (identified) that 0% of the simulated trials had early success, 5% late success. Thus this trial scenario produced an appropriate expected Type I error (α=.05,). The sample size of this scenario on average was 1000 patients, with half (500) in the OPT OUT arm. The average length of the trials under this scenario was 175 weeks— approximately 3 years of recruitment. Hence, our sample size of 1,000, in 3 years of recruitment, provides ample time and participants to identify project outcomes under all 3 scenarios.

Cost analyses for Hypothesis 3. We will conduct a cost-effectiveness analysis to explicitly document the relative costs and benefits of OPT OUT versus OPT IN. This analysis will be conducted in collaboration with Dr. Theresa Shireman at Brown University. Dr. Nazir and Dr. Shireman will manage the cost effectiveness analysis. Dr. Nazir will send Dr. Shireman de-identified data sets through secure electronic channels to ensure the protection of the confidentiality of participants. Our cost analytic framework generally follows the guidelines adopted by the Centers for Disease Control (CDC) in accordance with the consensus Panel on Cost-Effectiveness in Health and Medicine.[4-6] We will divide the analysis into two components: first, intervention only costs, and second, intervention plus short-term (<=6 months) costs post-discharge. The primary cost-effectiveness analysis will be set up as an incremental cost-effectiveness ratio (ICER). We anticipate that OPT OUT will be more costly and more effective than OPT IN. Incremental cost-effectiveness analysis identifies the marginal benefit of switching from one intervention to the other and is the ratio of the difference in costs divided by the difference in effectiveness between the two treatment options. The outcome assessed will be biochemically verified 7-day point prevalence abstinence. The ICER will indicate the added cost per additional quitter OPT OUT versus OPT IN, a metric that will allow comparisons to other smoking cessation economic studies. In designing these analyses, we considered using a societal perspective, as recommended by current national guidelines. The societal perspective, however, requires quality-adjusted life years (QALYs) as the denominator. Since this is a short-term study, we decided against attempting to estimate changes in QALYs, and focus instead on cost per quit.

The data derived for this cost analysis come from several clinical trials based in Kansas. In sensitivity analyses, we will adjust wages rates upwards to the national average. In order be able to generalize our findings from this one clinical trial to other populations, we will explore how the variation in counseling time and effectiveness influence the relative cost-effectiveness of the treatment strategies. Our analyses will vary time and effectiveness until breakeven points are achieved between the treatment options.

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