**PROJECT 2: Evaluating the Feasibility of Aerosolized Nicotine as an Aid to Quit Smoking**

**Background**

The following is a brief outline of a clinical trial that will evaluate the feasibility of a new medical device called QUITNOW, which is an aerosol nicotine delivery system (similar to a vaping pen) that slowly titrates down nicotine over time with the intent to help users quit smoking cigarettes. In this context, feasibility implies the following two things when the device is used in the way it is intended for the purpose of quitting smoking: 1) Use of the device by daily smokers presents no immediate safety concerns; and 2) There is a reasonable probability that the device could be beneficial. In short, a positive indicator of feasibility is an adequate balance between risk and potential for benefit. If the device is considered feasible then a logical next step would be to conduct a randomized, controlled trial to test the efficacy of the device for quitting smoking. Thus, the following study is considered to be a pivotal step in the further development of QUITNOW.

The description of the study below includes details of the safety monitoring rule that will be used to evaluate the first indicator of feasibility. A plan is also included for assessing the 2nd indicator of feasibility, which his related to the potential for benefit from the device. The statistical plan for the 2nd objective involves an exercise that is at the intersection of frequentist and Bayesian inference. Although considered controversial to some statisticians the exercise asks you to conduct an analysis of the “frequentist operating characteristics of the Bayesian design.” In other words, the exercise asks you to consider the changes of making the wrong decision related to the potential for benefit of this new device and is reflective of the type of question you might receive about such a study from the Food and Drug Administration (FDA).

**Assignment Description**

Your task is two-fold:

1. To reproduce the safety monitoring rule described in the protocol
2. To reproduce the simulation of frequentist operating characteristics of the Bayesian design as described in the excerpts from the study protocol shown below

In addition to writing the program code to reproduce the trial design details, you should present your results in a written report using RMarkdown that includes the following elements:

1. A complete description of the Bayesian methods used in the analysis, including how Bayes rule is used to find the posterior distribution in question
2. A detailed description of how your program is designed, including:
   1. The inputs and outputs
   2. The methods that operate on the input to produce the output
   3. An explanation of why these methods reproduce the trial design

**Study design overview:**

**Description of intervention:** QUITNOW is an aerosol nicotine delivery system (similar to a vaping pen) that slowly titrates down nicotine over time with the intent to help users quit smoking cigarettes. The user—who is a regular cigarette smoker---begins using QuitNow at the same time they are still smoking cigarettes, and then after a 1-week period “switches” from cigarettes to QUITNOW. After 23 weeks the user stops using QUITNOW. Success is defined as the user not smoking cigarettes or using QUITNOW at 26 weeks after quitting cigarettes (27 weeks after starting the study).

**Study Goal:** The primary objective of this study is to assess safety of the QUITNOW device and evaluate the potential for the device to help smokers quit. If this study doesn’t identify any substantial safety concerns, and suggests that QUITNOW might be beneficial then a randomized, controlled trial might be done in the future.

**Design:** The study is an open label, single-arm trial in daily smokers using a QUITNOW to quit smoking.

**Sample:** 50 adult (age >=18 years) daily smokers (>=1 cigarette/day for at least 1 year) who express willingness to attempt smoking cessation.

**Design:** The study is 27 weeks in length for each participant (Figure 1). The study begins with the Study Enrollment Visit at which point participants initiate use of QUITNOW. After 1 week of using QUITNOW the participant will quit smoking cigarettes on the target quit day. At 26 weeks post-quit (study Week 27) the participant will be assessed for the primary feasibility outcomes.

*Figure 1*

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| --- | --- | --- | --- | --- | --- |
| Time 🡪 | | | | | |
| Screening | Enrollment | 1-week pre-quit period (using both QUITNOW and cigarettes) | Quit Day @ 1 week (quit using cigarettes, using QUITNOW only) | Week 23 – quit using QUITNOW | Week 27 (26 weeks post-quit day) – PRIMARY EFFICACY OUTCOME |

**Primary Safety Outcome:** The occurrence of Grade 3 (severe) or greater side effects (nausea, vomiting, and headache whether related or unrelated to the device) and device-related events (e.g., burns or other effects on the participant from using the device).

**Primary Efficacy Outcome:** Continuous smoking abstinence across the last 4 weeks of the 26-week QUITNOW treatment period, biochemically verified by expired carbon monoxide < 7 parts per million.

**From the protocol statistical section:**

**Safety H1:** We hypothesize that less than 5% of participants will experience severe (or worse) side effects of device-related events while using QUITNOW over a 27 week period.

**Statistical Plan for H1:** We will use the Bayesian beta-binomial model with Beta(1,1) prior to estimate the posterior distribution for the proportion of QUITNOW users who have Grade 3 (severe) or higher side effects and device related events as follows. Let ϴ be the proportion with at least 1 Grade 3 or higher event. If P(ϴ ≥ 0.05) > 0.8 we would have concerns related to the safety of QUITNOW. Based on a Beta(1,1) prior, the posterior probability that ϴ is at least 0.05 would exceed 0.8 when 4 events are observed in 50 participants.

**Smoking H2:** We hypothesize that the abstinence rate is greater than 12.4% - the abstinence rate for NRT at 27 weeks post-target quit day (TQD) from meta-analysis of randomized-controlled trials.

**Statistical Plan for H2:** *See the appendix for complete details.* We will estimate the proportion who quit smoking cigarettes at Week 27 using a Bayesian beta-binomial model with Beta(1,1) prior as follows. Let ϴ be the proportion who quit smoking cigarettes at Week 27. In order for QUITNOW to be viable as a smoking cessation aid, there must be a high probability that ϴ exceeds the historical rate for smokers randomized to placebo in previous clinical trials. Therefore, the success criterion is . Simulation of frequentist operating characteristics shows that with 50 participants power exceeds 90% when the true abstinence rate is similar to e-cigarettes at 0.375 and has power of 0.74 when the QUITNOW is half as effective as e-cigarettes. Type I error is below conventional levels for a 1-sided test (< 0.025) for abstinence rates considerably worse than placebo (< .075) but Type I error is high at 0.275 when the abstinence rate is equal to placebo (0.124). For comparison, a 1-sided frequentist test (with alpha=0.025) of the null hypothesis that the abstinence rate is less than or equal to 0.124% has 99% power when QUITNOW is equivalent to e-cigarettes (0.375) but this test has a very low power of 22% when QUITNOW is half as effective of e-cigarettes (0.1875). Therefore, the Bayesian approach provides more power than the frequentist approach for smaller but still clinically relevant effect sizes but at the cost of inflated Type I error if the true abstinence rate on QUITNOW is equivalent to placebo from prior randomized trials.

**Frequentist Power for the Bayesian Design**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Prior** | | |
| **Scenario** | **Primary Analysis**  **Beta(1,1)** | **Optimistic**  **Beta(6,9)** | **Pessimistic**  **Beta(4,28)** |
| QUITNOW is equivalent to e-cigarettes, ϴ=0.375 | >0.999 | >.999 | 0.997 |
| QUITNOW is half as effective than e-cigarettes, ϴ=0.1875 | 0.743 | 0.97 | 0.457 |

**Frequentist Type I Error for the Bayesian Design**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Prior** | | |
| **Scenario** | **Primary Analysis**  **Beta(1,1)** | **Optimistic**  **Beta(6,9)** | **Pessimistic**  **Beta(4,28)** |
| ϴ=0.025 (much worse than placebo) | < 0.001 | 0.008 | < 0.001 |
| ϴ=0.05 | 0.003 | 0.102 | 0.003 |
| ϴ=0.075 | 0.031 | 0.332 | 0.004 |
| ϴ=0.10 | 0.122 | 0.568 | 0.023 |
| ϴ=0.124 (equivalent to placebo) | 0.275 | 0.762 | 0.086 |

**From the appendix:**

Simulated Frequentist Operating Characteristics for the Bayesian Efficacy Analysis

This study will enroll 50 participants at a single study center to estimate the proportion who quit smoking cigarettes at Week 27 based on a beta-binomial model. We selected a Bayesian approach to provide an estimate of the probability of quitting smoking with QUITNOW that can be compared with what is known from previous literature on abstinence rates among clinical trial participants randomized to placebo and e-cigarettes. Our projections for abstinence at 22 weeks in our study are based on meta-analyses of clinical trials are 12.4% for placebo and 37.5% for e-cigarettes.

*Statistical Plan*

Let ϴ be the proportion who quit smoking cigarettes at Week 27. In order for QUITNOW to be viable as a smoking cessation aid, there must be a high probability that ϴ exceeds the historical rate for smokers randomized to placebo in previous clinical trials. Therefore, the success criterion for this trial is:

*Selection of Priors*

The primary analysis will use a Beta(1,1) prior. An optimistic and pessimistic prior will be used for sensitivity analysis. The optimistic prior is centered near the estimate of in patients using e-cigarettes (0.40) whereas the pessimistic prior is centered near the estimate of in patients randomized to placebo in prior clinical trials (0.125).

| **Description of Prior** | **Prior Distribution** | **Prior Probabilities** | **Plot** |
| --- | --- | --- | --- |
| Non-informative | Beta(1,1) | -- | -- |
| Optimistic (similar to e-cigarettes) | Beta(6,9) | Mean=0.40  =0.99  95% CI: (0.18, 0.65) |  |
| Pessimistic (similar to placebo) | Beta(4,28) | Mean=0.125  =0.45  95% CI: (0.04, 0.26) |  |

*Simulation*

We conducted simulations of frequentist power under the following two scenarios:

1. QUITNOW is equivalent to e-cigarettes (ϴ=0.0.375)
2. QUITNOW is half as effective as e-cigarettes (ϴ=0.1875)

Type I error was explored for a range of values of ϴ below the success threshold of .124, i.e., representing QUITNOW as equal to or worse than placebo (0.025, 0.05, 0.075, 0.10, and 0.124).

*Simulation Design*

Let be the posterior probability from the beta-binomial model with prior distribution as described above and binomial likelihood (i.e., hypothetical clinical trial data) based on 50 patients and success probabilities (values of ϴ) described in the scenarios above.

Let index the number of simulations for a single scenario (e.g., QUITNOW is equivalent to placebo from prior randomized trials, ϴ=0.124, with a non-informative prior). We then defined the following quantity to study power and Type I error.

Where is the indicator function, returning 1 when the success criterion is met and 0 when the success criterion is not met.

For simulations where data were generated for values of ϴ > 0.124 this quantity represents statistical power; i.e., the proportion of simulations in which the success criterion was correctly met. For simulations where data were generated for values of ϴ < 0.124 this quantity represents Type I error; i.e., the proportion of simulations where the success criterion was *incorrectly* met.

For each scenario we ran N=10,000 simulations using R version 4.1.1. Data were generated using the rbinom() function and closed form equations were used to determine the beta posterior distribution. Posterior probabilities were estimated using the pbeta() function, and were rounded to two decimal places.

*Comparison to Frequentist Design*

After running the simulation of our Bayesian trial design, we compared the results to the power of a test of the null hypothesis vs. the alternative with 1-sided Type I error of 0.025. We evaluated power for the same true values of as we assumed in the simulation of the Bayesian design.