**Study Title:** Adaptive Interventions for Smoking Cessation in Lung Cancer Screening Program

**NCT #:** NCT02597491

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## 1.1 Objective of the Updated Statistical Analysis Plan

The objective of this updated statistical analysis plan (SAP) is to provide a description of the updated analytic strategy and the statistical methods that will be used to analyze the data for the Program for LUng cancer screening and TObacco cessation (PLUTO) Trial which uses a sequential multiple assignment randomized trial (SMART) design. The primary objective of the trial is to determine among incomplete responders to first stage tobacco longitudinal care (TLC) if medication therapy management (MTM) added to TLC is an effective approach for long-term tobacco cessation compared to TLC alone. The primary endpoint of this trial is a binary outcome of long-term tobacco cessation assessed 18 months after initial tobacco cessation treatment.

The primary statistical analysis plan was described in detail in the protocol paper (Fu et al., *Contemporary Clinical Trials*[1]). However, changes to the protocol and study status have necessitated updating the statistical analysis plan.

This updated SAP was prepared prior to unblinding of the data by statisticians and other members of the core PLUTO team who have been blinded to interim treatment comparisons for the duration of the trial.

Below we briefly summarize the status of the trial and some key blinded data that informed the preparation of this updated SAP.

## 1.2 Trial Status and Information That Informed the Updated SAP

### 1.2.1 Trial Status

The protocol underwent a number of minor changes throughout the study. Two key changes to the protocol are described below.

When the trial opened, participants were required to be scheduled for or have an order for first-time low dose CT for lung cancer screening. Due to fewer people undergoing lung cancer screening (both within the health systems studied in this trial and nationwide), we expanded the inclusion criteria. Eligibility was first expanded in January 2017 at the University of Minnesota and Minneapolis VA to include patients receiving repeat low dose CT for lung cancer screening, in addition to patients receiving first time scans. To further increase enrollment, we added a new site, Allina Health, in June 2018. In September 2018, criteria at the University of Minnesota (UMN) site were expanded to include all people who smoke who were eligible for lung cancer screening on the basis of their age and smoking history. Similarly, the criteria were expanded at the Minneapolis VA to include those who were eligible for lung cancer screening and a part of the lung cancer screening program regardless of their intention to receive another lung cancer screening.

Due to the COVID-19 pandemic-related safety protocols, saliva was no longer collected from participants after March 23, 2020. Thus, cotinine verification of smoking cessation was not able to be assessed after this date. From March 23, 2020 until May 19, 2020,

no participants were sent any biochemical verification. Beginning on May 19, 2020, participants were sent an iCO smokerlyzer to verify abstinence. Additionally, we attempted to send the iCO smokerlyzer to participants to whom we could not send a saliva kit from March 23, 2020 until May 19, 2020 even if those the data collection for those participants was out of window. We paused sending iCO smokerlyzers from July 2020 to December 2020 due to limited product availability.

### 1.2.2 Enrolment Summary

The first participant was enrolled on November 11, 2016; the last participant was enrolled on September 25, 2019. A total of 691 participants were enrolled across the three sites. Thirty-one participants withdrew prior to the baseline visits, and an additional 17 participants did not complete the outreach call after the baseline visit; thus, 643 participants were randomized to 4- or 8-week assessment of first stage TLC. A total of 510 participants were incomplete responders and were randomized to TLC vs. TLC + MTM; 126 participants were complete responders and randomized to TLC-Q vs. TLC-M. Seven participants were not randomized a second time. Thus, a total of 636 participants were randomized twice.

### 1.2.3 Summary of Pooled (Both Treatment Groups Combined) Follow-up Results

The final data collection was completed on May 1, 2021. Table 1 describes the data available from the Week 52 and Week 78 data collection calls. In general, data on abstinence is available if the participant only completed a mail-in survey (other secondary measures are not available). Among participants still alive, data are available on 86.8% (547/630) and 84.6% (529/625) of participants at Week 52 and Week 78.

Tables 2 and 3 summarize the number of participants randomized to each condition and the pooled (blinded), self-reported long-term abstinence.

*Table 1: Data availability at Week 52 and 78 data collection calls.*

| Status at data collection call | Week 52 n= | Week 78 n= |
|---|---|---|
| Complete | 517 | 494 |
| Missed | 63 | 77 |
| Incomplete | 0 | 0 |
| Participant withdrew from study | 15 | 16 |
| Participant refused call | 5 | 3 |
| Participant only did mail-in survey | 30 | 35 |
| Death on study | 6 | 11 |
| Total | 636 | 636 |

*Table 2: Number of participants randomized to each condition*

| Complete responder n=126 | | | | Incomplete responder n=510 | | | |
|---|---|---|---|---|---|---|---|
| Week 4 | | Week 8 | | Week 4 | | Week 8 | |
| TLC_M | TLC-Q | TLC_M | TLC-Q | TLC-M | MTM | TLC-M | MTM |
| n=32 | n=34 | n=32 | n=28 | n=133 | n=120 | n=123 | n=134 |

*Table 3: Pooled smoking outcomes at Week 52 and 78.*

| Smoking outcomes | Week 52 n= | Week 78 n= |
|---|---|---|
| 1) Smoked in past 7 days;<br>No<br>Yes<br>Missing | <br>187 (34.3%)<br>359 (65.8%)<br>90 | <br>191 (36.1%)<br>338 (63.9%)<br>107 |
| 2) Smoked in the last 30 days:<br>No<br>Yes<br>Missing* | <br>166 (77.9%)<br>47 (22.1%)<br>423 | <br>169 (78.2%)<br>47 (21.8%)<br>420 |
| 3) Smoked 7 consecutive days in last 6 months;<br>No<br>Yes<br>Missing* | <br>123 (64.7%)<br>67 (35.3%)<br>446 | <br>131 (67.9%)<br>62 (32.1%)<br>443 |
| 4) Smoked in 2 consecutive weeks in last 6 months:<br>No<br>Yes<br>Missing* | <br>115 (79.3%)<br>30 (20.7%)<br>491 | <br>130 (83.3%)<br>26 (16.7%)<br>480 |
| Prolong abstinence (#1, #3, and #4 =No) | 113/636 (17.8%) | 129/636 (20.3%) |

### 1.2.4 Sample Size Re-Estimation

In April 2019, the blinded statisticians were provided the pooled (both treatment groups combined) proportions of complete and incomplete responders and the proportion of those achieve long-term abstinence among incomplete responders in order to re-estimate sample size. Based on the observed pooled proportions, we estimated between 75-80% of the sample would be incomplete responders and of those incomplete responders between 10-15% would achieve long-term abstinence with TLC alone. The protocol paper outlines that we designed the study to have at least 80% power to detect a risk difference of 10 percentage points. Table 4 outlines the power for the primary aim under these assumptions. Based on these data, we changed the planned enrollment from 1,000 to 700.

*Table 4: Power estimates based on updated observed pooled proportions of the proportions of incomplete responders and proportion of incomplete responders achieving long-term abstinence.*

| n=700 | | | | | |
|---|---|---|---|---|---|
| **Proportion incomplete responders=80%** | | | **Proportion incomplete responders=75%** | | |
| | **TLC achieving long-term abstinence** | | | **TLC achieving long-term abstinence** | |
| **TLC+MTM long-term abstinence** | **10%** | **15%** | **TLC+MTM long-term abstinence** | **10%** | **15%** |
| **7.5% diff** | 73% | 62% | **7.5% diff** | 70% | 60% |
| **10% diff** | 91% | 84% | **10% diff** | 90% | 82% |

## 1.3 Summary of Changes to SAP

Based on the above information and additional data expected we made the following changes and clarifications to the SAP:

1. *Change in primary outcome:* Because saliva samples could not be collected for a portion of the sample due to COVID-19, biochemical verification could not be completed for all those self-reporting long-term abstinence. The primary outcome will be self-reported long-term abstinence at 78 weeks (18 months). This is defined as not smoking at all (even a puff) for the past 7 days and not smoking for 7 consecutive days during the past 6 months. As a supportive analysis, we will impute the missing biochemical verification data on those self-reporting long-term abstinence who declined biochemical verification, did not return the saliva/iCO smokerlyzer kits, or who were not sent a kit in window.

2. Adjusted analysis for primary and secondary aim: The enrolment for the trial was lower than anticipated. In particular, we initially anticipated between 650 and 750 incomplete responders whose outcomes would inform the analysis for the primary outcome. Based on the sample size re-estimation we anticipated between 525 and 560 incomplete responders. A total of 510 incomplete responders were randomized to second stage treatment. Similarly, initial power calculations assumed that there would be between 250 and 350 complete responders but only 126 participants were complete responders in this trial. In general, our other assumptions for the power calculations (e.g., long-term abstinence rate in the control group) were reasonable. To account for the under-enrolment, the primary analysis for the primary aim (comparison of TLC+MTM vs. TLC for incomplete responders) and secondary aim 1 (comparison of TLC-Q vs TLC-M) will be a logistic regression model with covariates for age, cigarettes per day, site (Minneapolis VA vs. others), first-stage randomization (4 vs. 8 week assessment) and second-stage randomized treatment group. In general, adjusted models tend to have higher power (although not guaranteed for a nonlinear model), but the interpretation of the

treatment effect estimate is challenging if there is treatment effect heterogeneity which is not accounted for in the model.[2] Similar adjusted models will also be the primary analysis for secondary aims 2 and 3. The unadjusted analyses described in the protocol paper will be a secondary analysis.

3. Methods to handle missing data: The SAP in the protocol paper specifies that "We will address missing response data using multiple imputation and additional sensitivity analyses." Multiple imputation will be done using the full conditional specification with predictive mean matching.[3] [4] [5] Covariates included in the imputation include age, gender, cigarettes per day at baseline, time to first cigarette at baseline, site, randomized treatment groups, and seven-day point prevalence at 4, 8, and 12 weeks, 6 months, and 12 months, in addition to 18 month long-term cessation. Note that some of these covariates may be missing as well and the full conditional specification enables one to impute these covariates as well. The imputation models for binary and continuous covariates will use logistic and linear regression models with main effect terms for all the other covariates. Twenty complete datasets will be imputed and the estimates from each the analysis of each complete datasets will combined using Rubin's combining rules. Participants who died will be recorded as a "failure," and we will not stochastically impute their endpoint. As a sensitivity analysis, we will also stochastically impute a cessation endpoint for those who died during the study. Note that only the primary endpoint will be imputed, imputation for other secondary endpoints will not be considered. Sensitivity analysis includes assuming those without data are still smoking and complete case analysis. Additional sensitivity analyses which may be considered (which do not assume that the missingness is ignorable) include joint models for longitudinal smoking cessation and nonresponse, pattern mixture models, and selection models.

4. Lung Cancer Screening Results: Secondary aim 4 addresses whether or not lung cancer screening results moderate smoking cessation outcomes. Due to changes in the eligibility criteria, participants may or may not have undergone lung cancer screening at any time during the 1 year of treatment provided by the study. For the purposes of this analysis, we will use the Lung RADS score from the first *screening* CT during the treatment period or just prior to the outreach call (the electronic medical record is queried up to 6 months prior to enrolment). When the Lung RADS score is considered an ordinal measure, those without CT scans will be considered to have a Lung RADS score of 0. As a sensitivity analysis, we will also group those participants with Lung RADS score of 1.

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[1] Fu SS, Rothman AJ, Vock DM, et al. Program for lung cancer screening and tobacco cessation: Study protocol of a sequential, multiple assignment, randomized trial. *Contemp Clin Trials*. 2017;60:86-95. doi:10.1016/j.cct.2017.07.002

[2] FDA (2019). Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biologics with Continuous Outcomes. *Draft Guidance for Industry*.

[3] Liu Y, De A. Multiple Imputation by Fully Conditional Specification for Dealing with Missing Data in a Large Epidemiologic Study. *Int J Stat Med Res*. 2015;4(3):287-295. doi:10.6000/1929-6029.2015.04.03.7

[4] Van Buuren, S. (2007). "Multiple Imputation of Discrete and Continuous Data by Fully Conditional Specification." *Statistical Methods in Medical Research* 16:219–242.

[5] Van Buuren, S. (2012). Flexible Imputation of Missing Data. Boca Raton, FL: Chapman & Hall/CRC.