CLINICAL RESEARCH PROTOCOL

IMBIO—Personalized Smoking Cessation
Randomized Controlled Trial

IMBIO, LLC.
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IMBIO-RCT Protocol

I. Project summary

Cigarette smoking is the leading preventable cause of premature disease and death in the United States[1]. Cigarette smoking affects nearly every organ of the body with cigarette smokers more likely than nonsmokers to develop respiratory and pulmonary diseases, lung and other cancers, and cardiovascular disease [1]. The total economic cost due to tobacco in the U.S. is over $289 billion a year, which includes at least $133 billion in direct medical care [1].

- The primary aim of this project is to clinically validate the impact and effectiveness of the IMBIO Patient Report in encouraging patients to make a quit attempt. We will do this in a randomized control trial (RCT) by comparing the report to usual care--with and without a proven telephone smoking cessation session--on high-risk smokers behavior in the context of a lung cancer screening program.

It is hypothesized that incorporation of the IMBIO Patient Report into lung cancer screening can improve a patient's readiness to make a quit attempt, and increase their use of smoking cessation Quitline and/or other smoking cessation resources, including medications. More specifically, it is further hypothesized that incorporation of the IMBIO Patient Report into smoking cessation counseling methodology can improve the behavioral intervention component of the Health Belief Model [38]. The IMBIO Patient Report would be the only smoking cessation product available to patient's that provides truly personalized information and comparative detail.

II. Background

Cigarette smoking is the leading preventable cause of premature disease and death in the United States[1]. Cigarette smoking affects nearly every organ of the body with cigarette smokers more likely than nonsmokers to develop respiratory and pulmonary diseases, lung and other cancers, and cardiovascular disease [1]. The total economic cost due to tobacco in the U.S. is over $289 billion a year, which includes at least $133 billion in direct medical care [1].

Recent U.S. government reimbursement decisions to provide lung cancer screening for high-risk current and former smokers are aimed at detecting lung cancer at an earlier stage when it can be more effectively treated. In 2013, based mainly on the results of the National Lung Screening Trial (NLST), the U.S. Preventive Services Task Force (USPSTF) concluded "with moderate certainty that annual screening for lung cancer with low density CT is of moderate net benefit in asymptomatic persons who are at high risk for lung cancer based on age, total cumulative exposure to tobacco smoke, and years since quitting smoking." [2] As a result, the USPSTF issued a Grade B recommendation for lung screening using low-dose CT for adults aged 55-80 years who have a minimum 30-pack year smoking history and currently smoke or have quit smoking within the past 15 years. [3]. Since January 2015, the Affordable Care Act (ACA) requires private insurers to cover such preventative services without cost sharing. In February 2015, the Center for Medicare and Medicaid Services (CMS) also announced its intent to reimburse providers for low-dose CT lung cancer screening of high-risk asymptomatic smokers. An estimated 7-10 million current and former smokers in the U.S. will be eligible for lung screening under these guidelines.

Tobacco dependence is a chronic condition, with most smokers making repeated quit attempts before they achieve long-term success [4,5]. Multiple studies have shown that the occasion of an annual lung screening exam may offer an important "teachable moment" for engaging a patient's interest in quitting, and encouraging them to make a serious quit attempt [6–8]. A retrospective analysis of 14,692 current smokers participating in the Lung Screening Study (LSS) arm of the NLST by Tammemagi et al showed that patients with suspicious findings on low dose CT scans quit smoking at higher rates regardless of whether the finding was found to be malignant [9]. Tammemagi's analysis showed that smoking cessation rates increased as screening findings became more serious or suspicious for lung cancer. Moreover, smokers in the NLST study who had negative screening exams continued smoking at the same rates as smokers in the general population, suggesting little

to no decrease in smoking cessation as a result of a "normal" exam. Nonetheless, concerns about smokers interpreting a negative screening exam for cancer as a "clean bill of health" and license to continue smoking persist, and many primary care physicians are skeptical about lung screening, given the high rate of false positive findings and resulting complications from diagnostic interventions[10,11].

Smoking cessation counseling has been shown effective at encouraging quit attempts and increasing rates of long-term abstinence, even in resistant populations such as long-term smokers [12]. Multiple analyses have shown that incorporating smoking cessation interventions, even as simple as a single counseling session, into lung cancer screening programs have the potential to improve cost effectiveness of screening [13–19] by 20% to 45% [15]. Proactive telephone Quitlines [20,21] may offer a cost-effective intervention and offer the possibility of a standardized approach to counseling across the country. However, further research is needed into the timing and types of cessation interventions that can have the most impact within the context of a lung cancer screening program, as reported quit rates are low in this chronic smoker population. Despite their elevated risk, 65.4% percent do not attempt to quit [1]. Methods to improve the effectiveness of smoking cessation counseling in this resistant population would be highly valuable [22].

Research supports that incorporating a patient's personal clinical status for future health risks, for example, pulmonary function test results [23–25], into smoking cessation education can increase quit attempts and long-term abstinence [26–35]. An increase in health concerns combined with enhanced self-control motivation improves the stage of readiness to quit [36]. While behavior change takes years to become established [37] "preliminary evidence suggests that the use of personal clinical feedback may improve motivation to quit smoking and, when combined with best practices treatment, could aid in the promotion of abstinence" [31].

In this project, IMBIO plans to clinically validate a personalized Patient Report Tool, based on a smoker's own screening CT images. The intent of the Report is to improve the impact of the "teachable moment" offered by lung cancer screening, by better communicating to smokers their personal clinical risks from continuing to smoke. These risks are based on the amount of emphysema present on their lung screening images, a clinical finding which is present in 30-40% of lung cancer screening exams. Emphysema is a clinical marker for important disease outcomes such as lung cancer, other types of cancer, cardiovascular disease, etc. independent of other risk factors including smoking history. In Phase I, Imbio designed a patient-centered report based on its FDA-cleared Lung Density Analysis (LDA) software for lung CT images that shows strong promise for increasing quit attempts by motivating patients to access smoking cessation resources including a quitline, other formal cessation programs, and/or cessation medications.

The IMBIO Patient Report (Figure 1) is based on the Health Belief Model [38] and includes five sections:

1) Image Section: visual feedback and quantitative results based on the quantitative image analysis of the patients own CT images.
2) Comparative Section: mapping the patient's lung health status to a corresponding cohort of participants.
3) Health Outcomes Section: information about the long-term consequences of smoking on a number of related health outcomes for the associated patient cohort.
4) Quit Now Section: stating the benefits of making a quit attempt
5) Outreach Section: contact information for smoking cessation support.

It is hypothesized that incorporation of the Report into lung cancer screening will improve a patient's readiness to quit, motivation to make a quit attempt, and increase their use of a smoking cessation quitline and/or other smoking cessation resources including medications. In addition, it is hypothesized that incorporation of the Report into smoking cessation counseling will improve the effectiveness of the behavioral intervention.

Background on Health Belief Model Methodology Incorporated into the Report

Patient-centered Report Design - The Report's novel image-based design reflects the constructs of the Health Belief Model, widely supported to trigger health-promoting behavior including smoking cessation [38]. The six constructs of the Health Belief Model are listed below with a description of how the Report addresses each construct.

- **Perceived susceptibility** *refers to a patient's belief in the likelihood of getting a disease or condition caused by smoking cigarettes*. The Report's Image section illustrates the patient's current lung health and

highlights their personal health risk based on information from his or her CT scan. The opportunity to see their own lungs was considered highly interesting and motivating to Phase I study participants. The image engaged the participants and drew them emotionally into the Report. To enhance understanding of the images, the typical colors used in Radiology to indicate healthy lung (dark gray) and disease (red), were discarded in favor of pink to indicate healthy lung tissue and black to indicate disease. The addition of an outline showing a torso to contextualize the lung images greatly improved the participants' comprehension.

- **Perceived severity** *refers to a patient's beliefs about the seriousness of the illnesses that they risk contracting due to smoking cigarettes*. The Report's Comparative section places the patient in a cohort that highlights how the patient's health compares with the large population of smokers who in the NLST study. The patient will also see, in the Health Outcome section, detail on long-term health outcomes of their corresponding NLST cohort, personalizing the impact of smoking on their overall health. The fact that patients are at increased risk for such debilitating outcomes as lung cancer and other cancers, and even mortality from continued smoking personalizes and underscores the severity dimension. Presenting these risk factors graphically dramatically improved the understanding of the related health risks by Phase I participants.
- **Perceived benefits** *refers to the benefits of quitting smoking cigarettes*. The Report's Quit Now section highlights the benefits to the patient if they stop smoking. The section outlines how their health will improve both in the short and longer-term [39], and focuses on those outcomes considered most important to the Phase I participants. An additional outcome from Phase I was the need to create multiple versions of this section corresponding to milder, intermediate and more extensive emphysema, such that the potential benefits of quitting smoking are perceived as realistic for the particular individual.
- **Perceived barriers** *refers to real or imagined barriers for the patient to quit smoking cigarettes*. The Report Outreach section includes personalized contact information for a quitline. It strongly emphasizes the benefits of accessing smoking cessation resources and the increased likelihood of long-term success via multiple quit attempts. It frames past quit attempts as learning experiences and notes that those who keep trying have a high likelihood of quitting. The Phase I participants were very concerned about who would answer the phone, and wanted to know if the counselor on the other end would be a past smoker. Most participants expressed reservations about calling, and said that they did not want to be judged. The Outreach section addresses these concerns via supportive language and information about what can be expected from the phone call.

- **Cues to action** *refer to the belief that a cue, or trigger, is necessary for prompting engagement in health-promoting behaviors*. The lung cancer screen, CT scan, and the Report listing information on accessing smoking cessation, are cues to action, which motivate the patient to quit smoking.
- **Self-efficacy** *refers to the individual's perception of his or her ability to quit smoking.* Multiple sections of the Report help build patient confidence in their ability to quit smoking. The Report stresses the importance of persevering and notes that successful quitting often follows multiple quit attempts.

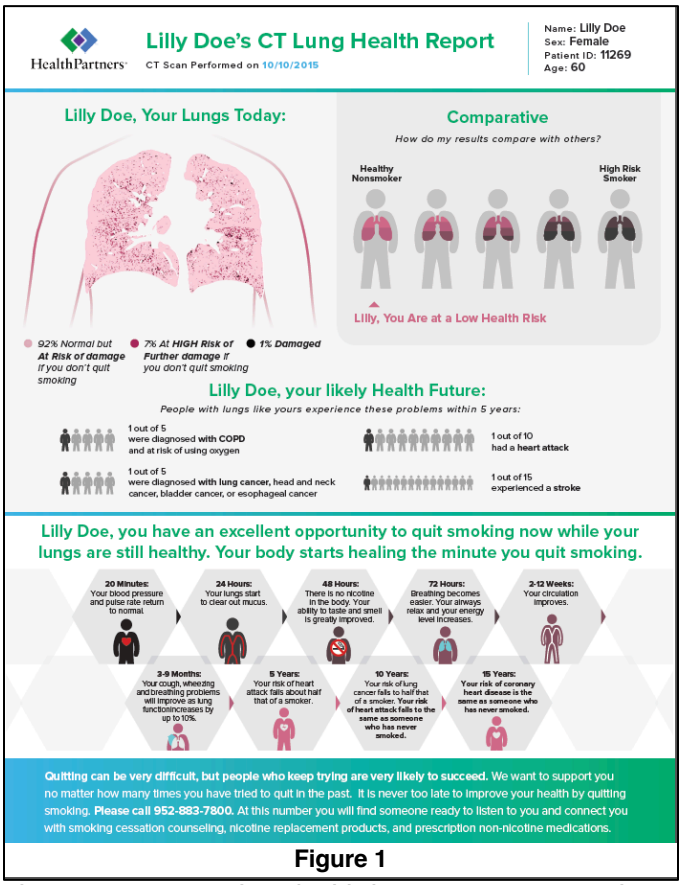

Figure 1

As noted previously, lung cancer screening programs have excellent potential to provide a teachable moment. McBride and colleagues recommend the consideration of three characteristics prior to defining an event as a teachable moment. These include the impact of: (1) the event on risk perceptions and outcome expectancies, (2) the emotional response associated with the event, and (3) impact of the event on social role and self-concept [40]. Making the impacts of smoking more visible to the patient through an emphasis on areas of emphysema in the Image section, in addition to the Comparative and Heath Outcomes sections, will significantly increase the likelihood that the patient will have an awareness of smoking risk and an emotional response associated with lung cancer screening.

While the Report builds on the teachable moment and is hypothesized to create a 'cue to action', behavior change is not often a single event. The Stages of Change model [41] outlines how a change in behavior can occur gradually from a patient being uninterested (precontemplation) to considering a change (contemplation), to deciding and preparing to make a change (stages of change). The Report's five sections help ensure that the patient is engaged at their current "stage" and motivated to move through subsequent stages toward lifelong change. For those patients in the precontemplation stage the image and comparison section will increase engagement. Those in the contemplation stage may focus more on the Outreach or Quit Now section. In the preparation stage, patients will find encouragement in the Health Outcomes and Quit Now section. As patients enter the action stage they will uncover support in the Outreach section. The final stage of maintenance and relapse prevention will be supported by services listed in the Outreach section and through yearly lung cancer screens. Each year the patient will receive a lung cancer screen and their Report; this cycle will further increase the likelihood that the behavior change of smoking cessation is established long-term [41]. While yearly lung cancer screens may support long-term change, testing the impact of yearly lung cancer screen with the Report is beyond the scope of this Phase II project, which assesses one lung cancer screen.

Background Information on IMBIO's Quantitative Image Analysis

It is well established that the presence of CT-detected low attenuation areas in the lung parenchyma is an important risk factor for lung cancer and other comorbidities of smoking such as pulmonary and cardiac disease. While a causal relationship is not presumed, it is known that chronic obstructive pulmonary disease (COPD), lung cancer, and other smoking-related diseases share common pathogenic mechanisms, including chronic inflammation, oxidative stress and impaired mucociliary function. Multiple studies in large patient populations have established a strong relationship between the amount of low attenuation areas present on a CT exam and a patient's risk for developing lung cancer [42–47]. These studies revealed that low attenuation areas is an important risk factor for lung cancer, independent of other factors including a person's age, gender and smoking history.

CT typically provides excellent anatomical detail with highly reliable image quality, and is thus amenable to quantitative techniques for detecting and characterizing the presence and the extent of low attenuation areas. Li et al. evaluated 565 lung cancer screening exams by computer-aided quantitative assessment of the percentage volume of the lung having low attenuation [42]. This study found that the amount of low attenuation lung tissue was an independent predictor for lung cancer risk, even after adjusting for smoking status and pack-years of smoking. Mets et al. developed a risk score calculated from the relative volume of low attenuation lung tissue under combined with other patient-specific clinical data such as BMI and smoking history to identify patients with clinically significant airflow restriction in a lung screening population [54], which has also been shown to predict important outcomes [48].

Imbio's quantitative lung analysis will automatically analyze a chest CT and quantify the percentage of lung volume with low attenuation. The algorithm, as a first step, automatically segments CT lung images into voxels corresponding to lung parenchyma and voxels corresponding to other tissues or background noise. A total volume of lung parenchyma is calculated for the patient. Low attenuation voxels are then identified based either on a dual-threshold technique or a classifier trained to identify radiologist-confirmed low attenuation areas of varying severity. Once low-attenuation voxels are identified, the total percent of lung with low attenuation can be calculated.

III. Study Aims

Primary study endpoints

- **Calling a Quitline number.**

Secondary study endpoints

- **Smoking cessation as measured by salivary cotinine testing.**

IV. APPROACH & STUDY DESIGN

Phase I Summary

In the earlier pilot project, Imbio designed a report that would increase a patient's motivation to make a quit attempt following a lung cancer screen by showing them the impact of smoking on their overall lung health (See complete Phase I final report in Appendix 1).

All goals of the pilot project were successfully achieved**,** via multiple rounds of interviews and focus group discussions conducted with high-risk smokers recruited by the HealthPartners Institute. Multiple versions of the Report were created and tested in the qualitative research using historical screening images for the Image section and fictional risk metrics for the Comparative section. Information gathered from each round informed the design of the subsequent round to improve participant comprehension and increase emotional impact of the Report.

The final round of focus groups, a questionnaire incorporating the Contemplation Ladder and Smoking Hazard scales, as well as a Self-efficacy Scale was used to assess the overall psychological impact of the Report design. Responses supported the hypothesis that a personalized version of the Report would likely have a positive impact on a participants' motivation to make a quit attempt, by increasing their hazard perception, and strengthening their belief in their ability to quit. Final focus group feedback indicated that participants were engaged by the Report and were very optimistic about its potential impact on smokers. Participants felt confident the Report would encourage smokers to make a quit attempt, especially when included as part of a smoking cessation discussion with a medical professional.

In conclusion, all milestones were successfully completed for the Phase I pilot. The Report design was dramatically improved for comprehension, personalization, and motivational content and design, and shows strong promise to increase quit attempts by motivating patients to access smoking cessation resources including a quitline, other formal cessation programs, and/or cessation medications.

Randomized Control Trial Study Design

The RCT will enroll approximately 400 self-selecting participants (200 at HealthPartners, and 200 at The University of Michigan) using a 2 by 2 factorial design from lung cancer screening programs at HealthPartners and the University of Michigan Heath Services.

INCLUSION CRITERIA:
Specific Inclusion Criteria (based on NLST guidelines) include the following:

- Age 55-74
- Smoking history of ≥ 30-pack years
- Currently actively smoking cigarettes
- Ability to read, write and communicate in English
- Screening CT scheduled at the HP Specialty Center (401 Phalen Blvd. St. Paul)
- Available by telephone for counseling and/or follow-up communications

EXCLUSION CRITERIA

- Clinically significant health problems that make projected lifespan ≤ 2-years
- LungRads Category 3 or 4 resulted out on screening CT

Recruitment and Consent - Randomized Controlled Trial participants will be recruited through the University of Michigan (200 participants) Health System and the HealthPartners Institute (200 participants).

- At HealthPartners, patients scheduled at HealthPartners Specialty Center will be given an informational flyer and consent form with return envelope during check-in for their Screening CT.
- Patients interested in participating in the study will be asked to contact the study coordinator by telephone within 72-hours (3-days) of their CT scan. During that call the coordinator will review the study requirements, read the consent form to the participant and attest to the patient's willingness to participate in the study. Participant will be asked to mail the last (signature) page of the consent to the coordinator in the envelope provided for back up hard copy.
- Consent forms will specifically request permission to share actual CT images with IMBIO in order to print a Patient Report based on the patient's own CT images. Specific permission will also be sought to share the Patient Report CT screening results with Mayo TTS and the Quitline representative.
- Following the screen, a radiologist will analyze the CT scan image and send the results to the patient's PCP. If the scan is read as a category 1 or 2 in the Lung CT Screening Reporting and Data System (Lung-RADS) [49], patients who have consented to study participation will be randomized to one of four treatment arms. If the scan is read as a category 3, 4A, 4B, or 4X in Lung-RADS the patient will be contacted by their primary care physician's office and told to schedule a follow up appointment. They will be sent a letter informing them they are not eligible for participation in the study after ordering physician has notified them of results and follow-up plans.

Randomization
Upon attestation of consent, eligible participants will be randomly assigned to one of four conditions using a central RedCap database:

1. Usual Care (w/ MN Quitline phone number);
2. Usual Care + Report (w/ IMBIO Quitline number);
3. Usual Care + Counseling; Or
4. Usual Care + Report (w/ IMBIO Quitline number) + Counseling incorporating results of report.

Those patients randomized to receive the Report will have their radiology images loaded onto a secure flash drive by radiology staff. The images will be uploaded into a HIPAA-compliant web-based portal hosted by IMBIO for processing and generation of the Reports, which can then be downloaded and printed.

Randomization letters, usual care letters and/or reports (Groups 2 & 4) will be mailed to participants. (For participants randomized to Groups 1 & 3, generation and mailing of reports will be delayed until study participation has finished.)

Synopsis of Treatment Arms

Usual Care - Subjects participating in lung cancer screening through HealthPartners and the University of Michigan Health System are referred for screening from their primary care physician (PCP). HealthPartners and the University of Michigan Health System require PCPs to document in the medical order system that current smokers who require a lung cancer screen have been offered smoking cessation counseling prior to providing the screen, in accordance with CMS guidelines [50]. Once a patient is cleared for screening, they are able to schedule an appointment at an affiliated lung cancer-screening site. Following radiologist reading of the scans, eligible study patients randomized to the usual care group will receive a standard results letter in the mail notifying them of screening results with a phone number that will lead them to the state of MN Quitline. The phone number will differ from the MN Quitline number in order to capture calling data. The phone number will provide a short voice message to recipients and then transfer them to the MN or MI Quitline depending on their location.

Tobacco Dependence Counseling

Counseling will consist of one 45-minute session by telephone to occur within two weeks (preferably no more than 10-days) after the lung cancer screen. Counseling sessions will be in accordance with established cessation counseling protocols developed at the Mayo Clinic. Tobacco Treatment Specialists (TTS) will have a complete list of local resources and will facilitate participant enrollment and/or use of medications at the time of the call.

Michael V. Burke, EdD.,Treatment Program Coordinator for the Mayo Clinic Nicotine Dependence Center will oversee the coordination and supervision of the Mayo Tobacco Treatment Specialists (TTS). Approximately three TTS will be trained to ensure consistent counseling methodology. TTS follow a validated approach when providing smoking cessation counseling over the phone [51–53]. TTS utilize a patient centered approach grounded in Motivational Interviewing skills [54–58] to elicit perceived benefits for stopping smoking and to enhance self-efficacy for stopping. Specific cognitive and behavioral strategies are collaboratively developed to engage evidence-based strategies for initiating a quit attempt and preventing relapse. A major emphasis of a call is to enroll the caller in formal cessation programs and/or convince them to use FDA approved medication as part of a quit attempt. At the close of each call, TTS confirm that callers are aware of the smoking cessation services available to them. Study participants who desire further smoking cessation support after their 45-minute session will be connected with the appropriate organization: HealthPartners Connect (HP commercial plan), or MN QuitPlan (HP Medicare). Study participants will be strongly encouraged to take advantage of available cessation resources. All participant feedback and questions on the follow up letter and/or Report will be documented. TTS will attempt to reach participants six times on different days and times of day before recording them as non-respondent.

IMBIO Patient Report- Research coordinators at the University of Michigan and HealthPartners will be provided access to Imbio's HIPAA-compliant web portal to upload image data and generate Reports. Following consent and lung screen, research coordinators will manually upload the study participants' images and download a resulting Report which will be mailed to the participants whose treatment arm includes the Report. Radiologists have been designated at both sites to review and approve the Report prior to mailing to participants.

Tobacco Dependence Counseling plus Patient Report- This arm will consist of the mailed report, which the TTS counseling call will incorporate into tobacco cessation discussion.

V. **Data Collection Processes**-

Outcomes will be assessed at 3 weeks, 3 months, and 6 months. Timing of outcome follow up will begin at time of consent attestation. There will be assessment of participant self-reported use of resources including enrollment in face-to-face cessation programs, calls to quitlines, use of medications, and other smoking cessation services. Participants reporting abstinence at three and six month follow up will be asked to submit saliva cotinine samples to confirm self-reports.

A survey to assess readiness to quit, motivation to make a quit attempt, use of a smoking cessation quitline, quit attempts and long-term smoking abstinence will be developed by Dr. Harry Lando. University of Minnesota Office of Measurements Services (Measurement Services) will administer follow up calls to assess readiness to quit, motivation to make a quit attempt, use of a smoking cessation quitline, quit attempts and long-term smoking abstinence. Measurement Services will be blinded to participant's conditions. All participants will receive follow up calls at 3 weeks, 3 months, and 6 months to assess calls to the quitline, readiness to quit, quit attempts, use of cessation aids (programs and medications), as well as current smoking following receipt of their lung cancer screen results.

Given the large number of subjects, Office of Measurement Services will input the survey into the Computer-Assisted Telephone Interviewing (CATI) Software[59] and train staff to ensure a consistent and effective approach.

Dr. Steve Hecht at the University of Minnesota will manage cotinine analysis. Participants reporting abstinence at 3 and 6 months will be asked to submit saliva samples by mail. A second consent form specific to cotinine collection will be mailed with the collection kit.

All participants will receive $20 after each of the first and second follow-up calls, and $70 after the final follow-up call. Participants who report abstinence will be provided an additional incentive of $50 to provide a saliva sample for a cotinine analysis. A maximum of $160 will be provided to participants as compensation for their time and as an incentive for their participation. Compensation will be provided as Target gift cards, mailed to patients address on record after confirmation of follow-up completion by University of MN Office of Measurement Services (OMS).

Data management - Data will be stored in a secured, centrally located REDCap database. Investigators will oversee the REDCap database setup, data management, audit and edit plans to ensure data accuracy and completeness, and creation of the study's codebook with precise definitions and coding of all variables. A double-checking mechanism will be set up to ensure data completeness and accuracy. Strategies are set up for handling missing data, which are described below.

VI. Data Analysis, Sample Size and Statistics - David Vock, PhD, a biostatistician with the University of Minnesota School of Public Health, will analyze data from the RCT. Similar to standard methods for factorial designs in other therapeutic areas, analyses to address the primary aims will be a test of the main effect of the randomized interventions (i.e., report type and counseling type). All analyses will be by intention-to-treat, and include all participants randomized, regardless of whether they are lost to follow-up. The primary outcome measures will be a dichotomous comparison of 24-hour quit attempts (yes/no) at the time of the three-week follow-up, three-month follow-up, and six-month follow up and subject-reported readiness to quit based on the contemplation ladder among those who have not quit smoking. Secondary outcomes include cotinine-verified abstinence at three and six-months and use of smoking cessation services (dichotomous outcome) at 3 weeks, 3 and 6 months. Initially assessment will focus on the main effect of Report condition (Report vs. Usual Care) averaging or "pooling over" the Counseling condition on the continuous (readiness to quit) and dichotomous outcomes (24-hour quit attempt, abstinence, use of smoking cessation services) using a two sample t-test of the difference in the mean response and two-sided Wald-type test [60] of the difference in proportions, respectively, with a 0.05 significance level. Exact tests (e.g., Barnard's exact test) may be used if the number of successes (e.g., quit attempts, abstinence) is

small. Separate analyses will be performed at each measurement time point (e.g., three-weeks, three-months, and six-months). A similar set of analysis can be performed to assess the main effect of the counseling condition. Logistic and linear models (for the dichotomous and continuous outcomes) with covariates for report condition, counseling condition, and their interaction will be used to assess if the Report and Counseling conditions significantly interact. If the interaction is significant, there will be an examination of whether there is a significant difference between the Report and Usual Care within each level of the Counseling condition. As an exploratory analysis to help guide future studies, a logistic regression model with quit attempt (yes/no) as the response will be utilized. Possible covariates include intervention group, gender, age, number of pack years, interest in quitting at baseline, risk perception at baseline, number of previous quit attempts, and findings from the CT scan, and their interaction with the Report condition. Similar models could be constructed for the other outcomes (abstinence, use of use of smoking cessation services). Additional linear regression models will be constructed for the other outcomes (readiness to quit). Additionally examination will be on whether or not changes in readiness to quit at 3 weeks mediate quit attempts, use of smoking cessation resources, and abstinence at 3 and 6 months using structural equation modeling.

Sample Size: The proposed RCT is powered for a main effects analysis of the Report (averaged over the Counseling condition) for the following outcomes a) at least one 24-hour quit attempt within 6 months of the CT scan b) accessing either formal cessation programs and/or FDA-approved medications within 6 months and c) readiness to quit as measures by the contemplation ladder.

Power for these primary hypotheses are shown in Table 2 assuming 400 total subjects under different assumptions concerning the average response within each of the randomized groups. A difference of 20% and 12.5% is considered between the Report and Usual Care conditions to be of interest for the percentage of subjects with at least one 24-hour quit attempt and accessing cessation programs/medication within 6 months. Similarly, an average difference of 1.5 on the contemplation ladder is considered meaningful. Table 2 indicates there is sufficient power to detect these differences and even reasonable power across many scenarios to detect smaller effects for the main effect of the Report. Additionally, Table 2 demonstrates that there is adequate power to detect a significant effect of the Report within each level of the counseling condition at the 0.1 significance level.

Concerning 6-month abstinence, differences were considered between the Report and Usual Care between 5-10% to be meaningful. As a Phase II study, it is not powered to detect a significant main effect for the Report for the 6-month abstinence outcome. However, Table 3 demonstrates that across a range of plausible scenarios there is sufficient power for a composite test of whether or not the probability of abstinence at 6 months is the same across all 4 arms and whether or not the Report + Counseling is different than Usual Care.

As part of the analysis, it is expected that Report Only compared to Usual Care will significantly increase readiness to quit, quit attempts, and accessing of programs/medications. It is also expected that the Report + Counseling will produce significantly higher 7-day point prevalence abstinence at 6 months than Usual Care with the other two conditions intermediate. In particular, it is expected that the combination of counseling and the Report will be more effective in increasing readiness to quit, quit attempts, use of formal programs and/or medications and abstinence than the other three conditions. Additionally, it is expected that 5% in the

	Percentage or Mean				Power to Detect a Significant Effect of Report		
Outcome	Usual Care	Report Only	Usual Care + Counseling Only	Report + Counseling	Main Effect (averaged over counseling conditions)	Within No Counseling Condition	Within Counseling Condition
24 hour quit attempts	20%	40%	40%	60%	98.7%	93.5%	89.3%
	20%	35%	35%	50%	89.2%	77.7%	69.4%
Accessing Services and/or Medication	5%	17.5%	17.5%	30%	92.4%	88.9%	67.6%
	5%	15%	15%	25%	81.2%	77.2%	55.1%
Readiness to Quit	6.0	7.5	7.5	9.0	99.9%	97.8%	97.8%
	6.0	7.0	7.0	8.0	93.2%	78.6%	78.6%

approved medications, or c) the mean readiness to quit on the contemplation ladder between the Imbio report and usual CT scan report. Power calculations assume total N=400 and the use of a two-sided test with a 0.05 significance level for the main effect and 0.10 significance level for the effects within each counseling condition level. The power calculation for readiness to quit assume a standard deviation of 2.9 on the contemplation ladder.

Usual Care condition will make a quit attempt (24-hour quit) versus 15% in the Report condition at the time of the 3-week follow-up. The Report will yield significantly greater percentage of subjects reporting a quit attempt at 3 and 6 months.

VII. Title 21 FDA Device Trial Regulations

The IMBIO **Patient Smoking Cessation Report** is currently preparing to undergo the proposed RCT in preparation for eventual FDA approval as a medical device. This trial will be run under the non-significant risk (NSR) section of Title 21 FCR 812.2(b) and will follow the abbreviated trial requirements contained therein. CFR 812.2(b) is uploaded with this application. Also uploaded is Title 21 CFR 56.111, which gives the IRB criteria for approval of NSR clinical device research under the abbreviated requirements associated with FCR 812.2(b).

The IMBIO Patient Smoking Cessation Report, as an NSR device, is not required to seek IDE approval through the FDA prior to starting the clinical trial proposed in this application. IRB agreement that this device qualifies as an NSR device will suffice in lieu of a formal IDE application, as long as said determination of NSR status is transcribed into formal IRB minutes.

This clinical trial will be monitored by the sponsor of the trial, IMBIO, LLC, in accordance with the monitoring requirements found in Title 21 CFR 812.46.

Following the conclusion of the clinical trial proposed in this application, the sponsor will approach the FDA for approval or clearance as a medical device.

VIII. Study Timeline

Phase II Work Plan	2016			2017												2018												2019							
	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct.	Nov.	Dec.	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct.	Nov.	Dec.	Jan	Feb	Mar	Apr	May	June	July	Aug.
Recruit RCT participants																																			
SUBMIT mayo IRB application (with questionaire developed in SA2)																																			
Training TTS																																			
IRB complete for U of MN, MI, and Mayo																																			
Install Imbio Software/determine approach																																			
Participant Lung screening																																			
Cessation counseling cond. 3-4																																			
Quitline support cond. 1-2																																			
3-week follow up call																																			
3-month follow up call																																			
6-month follow up call																																			
Disseminate research findings.																																			
Write Final Report																																			

IX. References

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