A211401-- REDUCING SURGICAL COMPLICATIONS IN NEWLY DIAGNOSED LUNG CANCER PATIENTS WHO SMOKE CIGARETTES

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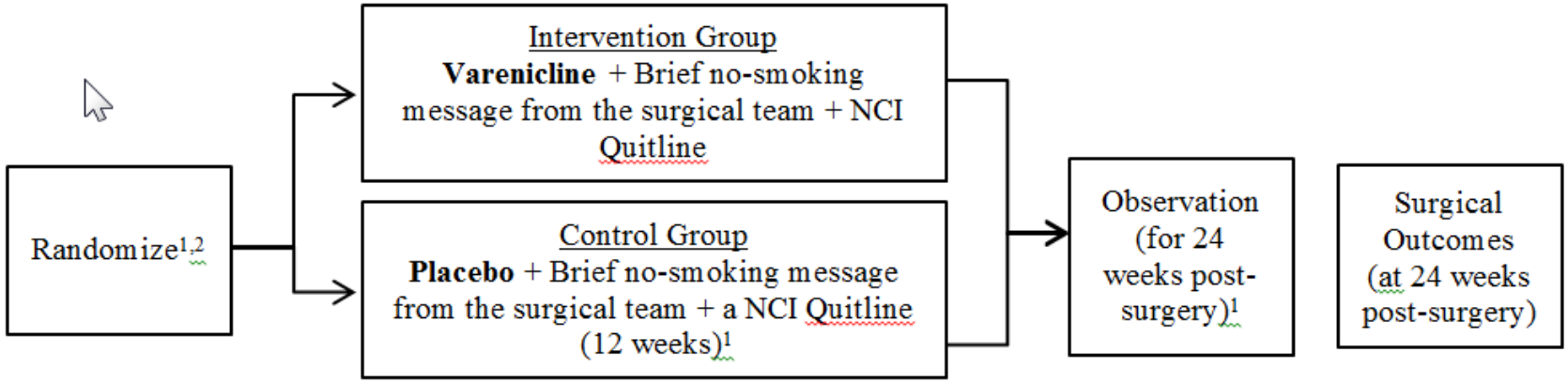
Study Schema



1 Tobacco use will be assessed prior to registration, at randomization, and every six weeks during treatment and observation until 24 weeks after surgery.

2 **Please note**: Baseline is at the time the surgical message is discussed with the cancer patient. Surgery must occur after the target quit date (TQD) defined at baseline and can be performed no sooner than 10 days after randomization and no more than twelve weeks after randomization.

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Overall Objective

To assess the effect of smoking cessation treatment on **surgical complications**, **QOL**, and **post-operative care**.

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Specific Aims:

Primary

- To determine if varenicline, when added to a behavioral intervention consisting of a brief clinician-delivered intervention with tobacco quitline follow-up, **decreases postsurgical complications through 24 weeks after surgery** in lung cancer patients who undergo surgery and are motivated to stop smoking.

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Secondary Objectives

- To compare changes from baseline to 12 and 24 weeks after surgery in the patient **quality of life** (LASA10) domains between the intervention (varenicline) and control group (placebo).
- To compare changes from baseline to 4, 8, 12 and 24 weeks after surgery in the patient quality of life related domains (**LASA**) for the **PHQ-9** and **SEQ12** between the intervention and control groups.
- To compare the proportion of patients 12 weeks and 24 weeks after surgery who **endorse** ("Was It Worth It") each treatment (intervention vs. control groups).
- To compare **post-operative care** (as measured by length of hospital and high dependency unit stay) between the intervention and control groups.
- To compare **treatment adherence** between the intervention and control groups.
- To compare **rates of smoking abstinence** between the intervention and control groups.

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Correlative Science Objectives

- To evaluate the predictive role of the nicotinic receptor gene cluster (*CHRNA5-CHRNA3-CHRNB4*) and *CYP2A6* genotypes in smoking cessation among lung cancer patients undergoing surgery.
- To evaluate the potential moderating effect of these cessation-relevant genotypes on smoking cessation treatment between the intervention and control groups.

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Considerations for subject enrollment

- Diagnosis of Lung Cancer
- Surgical consult
- Daily smoker for 6 months prior
- No Psychiatric illness which would prevent the patient from giving informed consent.
- No Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients who cannot swallow oral formulations of the agent.
- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

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Stratification Factors

Patients will be stratified into two groups based on the type of resection performed:

- Minimally invasive (such as Lobectomy or Robotic surgery)
- Other (such as bi-lobectomy or pneumonectomy)

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Treatment Assignments and Blinding

- 12 weeks of treatment – beginning as little as 10 days prior to surgery and up to 12 weeks prior to surgery
- TQD – 8 days after starting medication
- 12 weeks of follow up – post end of medication

- 1:1 Randomization based on stratification factors
  - Intervention Group:
    - **varenicline**
    - a brief no-smoking message from the surgical team
    - behavioral support provided by a telephone smoking quitline (NCI's 1-877-44U-QUIT) for 12 weeks.
  - Control Group:
    - **placebo**
    - a brief no-smoking message from the surgical team
    - behavioral support provided by a telephone smoking quitline (NCI's 1-877-44U-QUIT) for 12 weeks.

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Teachable Moment Training

- Surgeons and designated members of the surgeon's team will be trained and educated in the basics of smoking cessation counseling and delivery of the No-Smoking message to the surgical oncology patient.
- The training will be conducted via **Webinars** for convenience of the site study teams, and based upon a validated approach to clinician-delivered tobacco use intervention (Warner et al, Anesthesiology 114:847-855, 2011).
- A standardized script of key speaking points will be developed and utilized by all participating surgical teams.
- Study subjects will be provided with a folded **flyer** which will re-inforce the surgical team message as well as the quitline phone number
- All **training will be documented** and each site must have this training prior to study start up – for consistency.

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Dose Modification

Dose Level 0	**1.0 mg twice daily**
Dose Level -1	1.0 mg once daily
Temporary discontinuation	

- All missed doses should be considered as skipped and not delayed. That is, the duration of treatment must not continue past the original 12-week stop date.
- Patients may be re-challenged only one time for grade 3 events. That is, if a particular adverse event recurs after a dose reduction and re-challenge, varenicline/placebo will be permanently discontinued.
- If treatment is skipped for more than four weeks due to toxicity, permanently discontinue varenicline/placebo.

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Dosing

Agent	Dose	Route	Day	
Varenicline/Placebo	0.5 mg	Oral	Days 1-3	1 pill per day
Varenicline/Placebo	0.5 mg	Oral	Days 4-7	2 pills per day – Minimum of 8 hours apart
Varenicline/Placebo	1.0 mg	Oral	Days 8-84	2 pills per day – Minimum of 8 hours apart

- Recommendations:
  - Dosing should occur with 240 mL of water
  - Eat prior to dosing to decrease gastric upset.
  - There should be at least 8 hours between the morning and evening dosing.
  - If a dose is missed, the patient should take it as soon as s/he remembers.
  - If it is almost time for the next dose (within 6 hours), the patient should skip the missed dose and take the next one as scheduled.
  - Patients should not take a double dose of varenicline/placebo.

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Varenicline Safety data – Eagles Study*

- Design
  - 16 country multicenter
  - 4074 smokers with psych conditions
  - 3984 smokers without psych conditions
  - Triple dummy design:
    - Treatment groups: varenicline, bupropion SR, transdermal nicotine patch and placebo

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* - *Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, Ascher J, Russ C, Krishen A, Evins AE. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. Lancet 2016 Apr 22. doi: 10.1016/S0140-6736(16)30272-0 [Epub ahead of print]*

EAGLES STUDY* - AEs

- Primary safety endpoint:
  - *Composite of 16 neuropsychiatric (NP) AE's - anxiety, depression, feeling, abnormal, and hostility (all rated as severe), and agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, and completed suicide*
- Rate of **NPS AE's** was **similar** across the 4 groups with more AE's in the psych arm
- Rate of **drop out** due to NPS AE's was also **similar** across the 4 groups
- In the **non-psychiatric cohort**, the risk for the composite safety endpoint was **significantly lower** for varenicline-treated compared with placebo-treated participants.
- In the **psychiatric cohort**, risk differences between the active treatment groups and placebo were **not significant** (95% CIs included zero).

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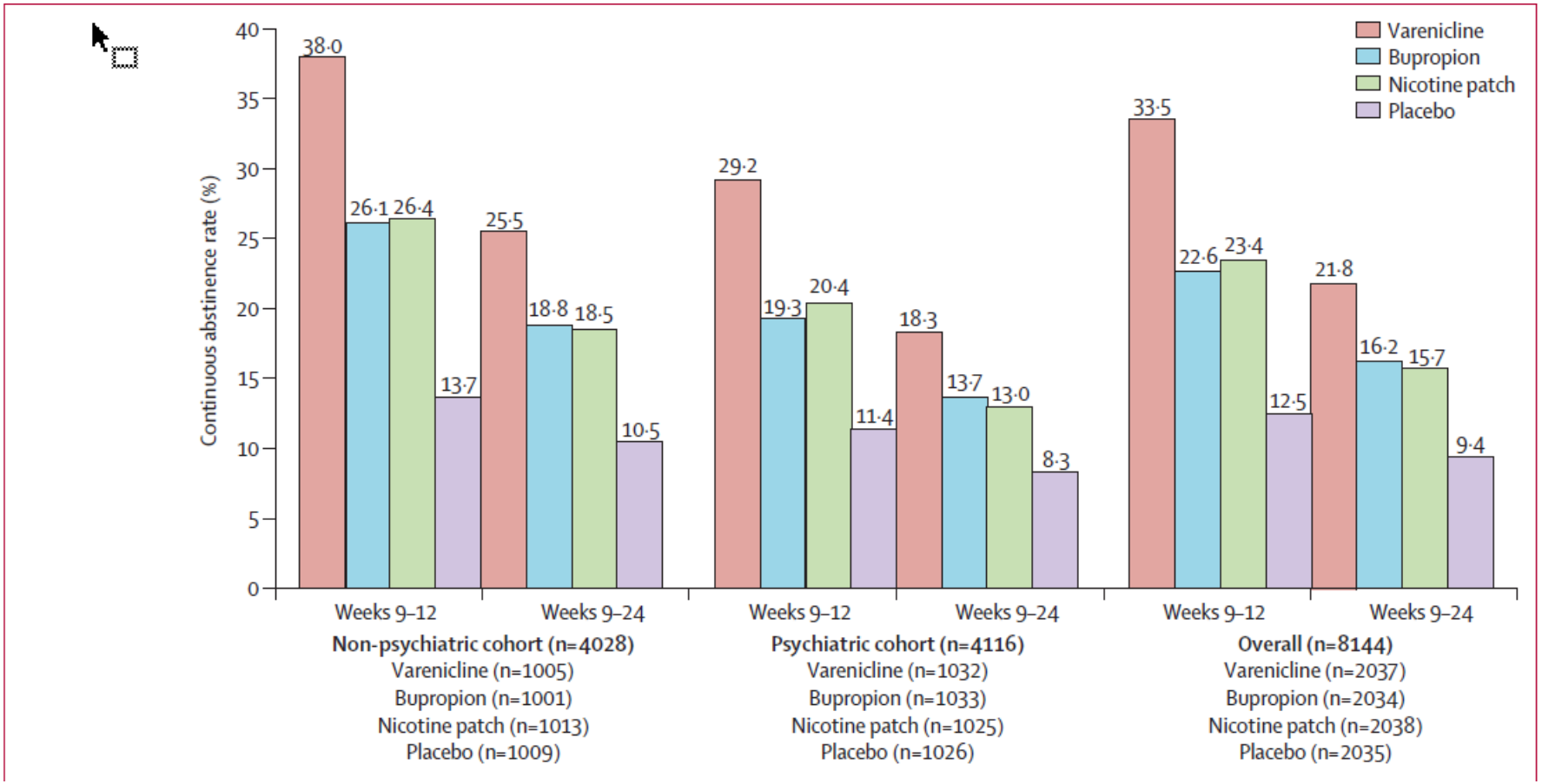
Continuous Abstinence:



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Study Calendar

	Consent /screen*	Baseline	Day of Surgery**	Week 6	Week 12	Week 18	Week 24
Visit Type	In person	In person	In person	In Person	Phone/in person	Phone/In person	In person
Med Hx/PE	X	X					
Screen/ registration	X						
AE/Con Meds		X**	X**	X**	X**	X**	X**
Quit Message		X					
Quitline		X					
Study Med		X	X	X			
PHQ-9		X		X	X		X
Tobacco Use Assessment		X	X	X	X	X	X
SEQ-12		X		X	X		X
LASA		X	X	X	X		X
Saliva		X	X	X	X*	X*	X*
Blood		X					

* - visit can be completed over the phone, but the patient must return to the site for a salivary cotinine sample (physician visit not required)

** - can be collected as self report or record abstraction

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Surgical Adverse Events – primary endpoint

- 30-day mortality
- 30-day re-hospitalization
- 1-year mortality
- Anastomotic failure
- Anesthesia-related respiratory complications
- Bleeding (transfusions > 5 U)
- Coma (> 24 hours)
- Deep venous thrombosis/ thrombophlebitis
- Failure to wean from the ventilator
- ICU readmission
- Impaired bone healing
- Implant loss (breast reconstruction)
- Increased postoperative pain
- Renal insufficiency/failure
- Return to operating room
- Sepsis/septic shock
- Stroke/cerebral accident
- Surgical infection (organ space)
- Surgical site infections
- Urinary tract infections
- Increased postoperative surgical stay
- Increased scarring and asymmetry
- Intubation (unplanned)/re-intubation
- Lower rates of successful digital replantation (microsurgery)
- Myocardial infarction
- Pneumonia
- Prolonged intubation
- Prolonged ventilator support
- Pulmonary complications
- Pulmonary embolism
- Reduced skin flap survival
- Vascular complications
- Vein graft failure
- Venous thromboembolism
- Ventilator (> 48 hours)
- Wound healing (delayed)
- Wound infection (sternal)
- Wound infections (superficial and deep)

These complications were identified as being sufficiently numerous from an investigation of the national surgical database (ACS-NSQIP). They will be defined using the General Thoracic Surgery Database (GTSD) for study purposes.

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Questions

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