iNudge Statistical Analysis Plan

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Background and Rationale

The present project is an implementation project to determine the effectiveness of a Behavioral Economics (BE) informed EHR nudge intervention to increase timely receipt of comprehensive molecular test results before 1L therapy by integration of concurrent tissue and plasma molecular testing in patients with newly diagnosed mNSq NSCLC.

The development of targeted therapies has changed the treatment paradigm for non–small cell lung cancer (NSCLC). With the growing number of FDA approved targeted therapies, current NCCN guidelines recommend comprehensive molecular genotyping, defined as detection of mutations in seven genes EGFR, ALK, BRAF, ROS1, MET, RET, KRAS, Her2 and NTRK testing prior to first line (1L) therapy for all newly diagnosed patients with metastatic non-squamous (mNSq) NSCLC to enable the delivery of personalized therapy.[i] [ii] Furthermore, the emergence of immune-checkpoint inhibitors has amplified the importance of molecular genotyping in the care of these patients because patients with actionable genomic alterations rarely respond to immunotherapy, even in the presence of high PD-L1 expression and should be preferentially treated with targeted therapy.[iii] In addition, there is a growing body of evidence that introduction of targeted tyrosine kinase inhibitors after immunotherapy may be associated with higher rates of immune related adverse events, even after discontinuation of immunotherapy.[iv] Additionally, in previous studies, amongst patients with a mutation in a NCCN-listed gene, exposure to targeted therapy has been shown to be associated with improved overall survival.v Given these considerations, upfront tumor genotyping is now considered an essential step in guiding treatment decisions for all patients with mNSq NSCLC, prior to 1L therapy. Despite the critical importance of molecular testing in patients with advanced NSCLC, numerous barriers impede timely completion of testing prior to initiation of 1L systemic therapy. [vi] [vii] [viii]

The overarching goal of this current trial is to expand the application of the BE informed nudges, which includes a Best Practice Advisory (BPA) and Electronic Decision Support Tool (e-CDS) approach, which has been operationalized within Epic, the EHR used at UPHS, to six satellite hospitals. Our central hypothesis is that this approach will dramatically increase adoption of comprehensive molecular testing and enhance the delivery of molecularly informed first-line therapy in patients with newly diagnosed metastatic non-squamous NSCLC. Molecular testing will be defined as i) comprehensive: EGFR, ALK, BRAF, ROS1, MET, RET, KRAS, Her2 and NTRK testing, ii) incomplete: <6 genes tested, and iii) no testing performed. Clinically actionable mutations will be defined as an alteration in one of the seven genes on the comprehensive gene list with an FDA approved targeted therapy in the 1L setting, plus KRAS G12C, EGFR exon 20 insertion, and ErbB2 mutations. Molecularly informed first line therapy will be defined as one that is informed by results of NGS, obtained by plasma, tissue or both.

The trial will use a prospective stepped wedge cluster randomized design while incorporating baseline data in the control condition prior to the initiation of the stepped wedge.

Figure 1. Stepped-wedge trial design with estimated patient enrollment

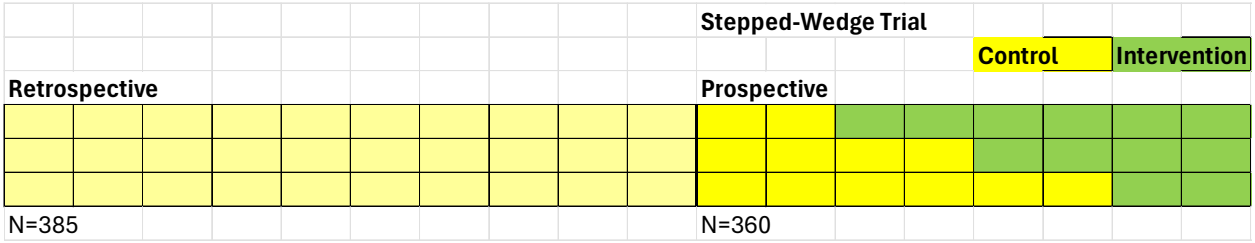
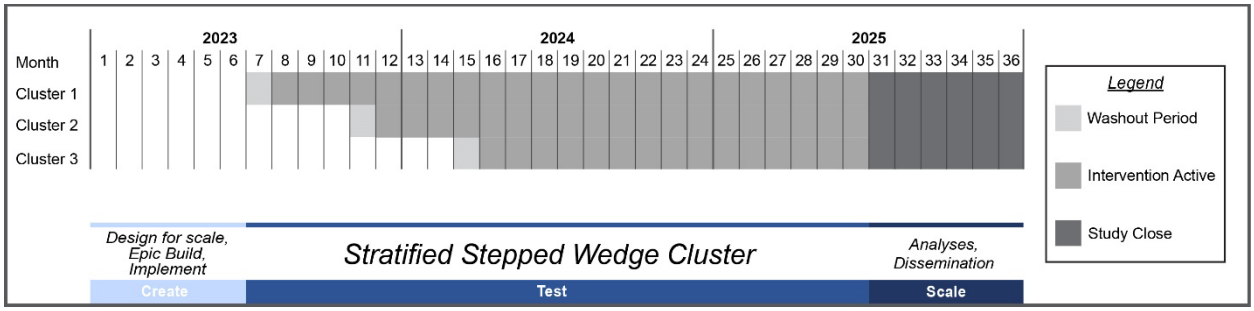


Figure 2. Stepped-wedge cluster design with washout and intervention timeframes



The design of this trial will include 3 clusters, representing the 6 community hospitals. There will be an initial period in which no clusters are exposed to the intervention. Subsequently, at regular intervals (the "steps") one cluster (or a group of clusters) will be randomized to cross from the control to the intervention under evaluation. This process will continue until all clusters have crossed over to be exposed to the intervention. At the end of the study there will be a period when all clusters are exposed. Data collection will continue throughout the study, so that each cluster will contribute observations under both control and intervention observation periods.

Objectives and Hypotheses

Objective 1: In a stepped wedge cluster randomized trial of patients with newly diagnosed metastatic NSCLC, test the effectiveness of a BE informed EHR nudge intervention to increase timely receipt of comprehensive molecular test results before 1L therapy by incorporating concurrent tissue and plasma-based molecular testing into the workup of newly diagnosed patients.

We hypothesize that comprehensive molecular testing before 1L therapy will be higher under the intervention (EHR-based nudges) than under the standard of care condition.

Design and Randomization

- Stepped-wedge cluster-randomized trial, with standard of care (No EHR nudge) transitioning to intervention (EHR based nudges)
- Hospitals (clusters) will be randomized to the order in which they start the intervention phase.

Population

Target Population

This stepped wedge cluster randomized trial will be conducted across newly diagnosed patients with mNSq NSCLC treated at Penn Medicine that comprise 3 clusters (sites):

1) Penn – New Jersey (Princeton Medical Center (PMC), Penn Medicine at Cherry Hill (PMCH), Penn Medicine at Washington Township (PMWT), and Penn Medicine Voorhees (PMV)), 2) Lancaster General Hospital (LGH), 3) Penn Presbyterian Medical Center (PPMC).

Inclusion Criteria

a) Patients with histological, or cytological diagnosis of mNSq NSCLC who have not yet received systemic treatment for metastatic disease.

b) Patients must be seen at LGH, PMC, PPMC, PMCH, PMWT, or PMV for mNSq NSCLC

Exclusion Criteria

a) Incomplete staging information.

Vulnerable Populations

a) Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

Primary Outcome and Analytic Methods

Primary outcome

Objective 1: The primary endpoint is receipt of comprehensive molecular test results prior to 1L therapy for patients with mNSq NSCLC. This (binary) outcome encompasses successful completion of concurrent tissue and plasma based molecular testing and the ability of the patient and oncology care team to have all necessary information to collaboratively arrive at the optimal treatment approach. We anticipate that approximately 80% of patients in the interventional arm will have molecular test results available prior to initiation of first line therapy. The primary outcome will be assessed by review of clinician documentation (e.g., progress notes) within the electronic medical record (EHR). Baseline data will be collected from all sites. Baseline data will also be collected from the PCAM site and will serve as the contemporaneous academic benchmark for molecular testing. Molecular testing rates will be assessed, proportion of patients who undergo

comprehensive molecular genotyping prior to start of 1L therapy for mNSq NSCLC will be tabulated (Comprehensive testing will be defined as testing of all NCCN recommended biomarkers). Proportion of patients receiving targeted therapies when therapeutically targetable alterations are detected will be tabulated on a quarterly basis.

Primary analytic sample

The primary analysis will follow the Intention-to-treat (ITT) principle, such that all patients meeting eligibility criteria during the open (non-washout) periods will be included in the analysis.

Preliminary Analysis

Prior to performing analyses, we will apply standard data screening/cleaning procedures that will help us: (i) identify data-entry errors and outliers, (ii) assess the extent and patterns of missing data, and (iii) verify statistical modeling assumptions (e.g., normality, homogeneity).[ix] In all analyses, we will assess underlying assumptions using residuals, influence diagnostics, and graphical displays.

Primary analysis

The primary outcome for objective 1 is binary and will be analyzed using mixed-effects logistic regression. As fixed effects, the model will include the treatment status of the patient's cluster, as well as an ordinal or continuous variable representing time. It will also include cluster-level (two clusters for each of the PA sites and one for all NJ sites) random intercept and slope terms for treatment status, which will be considered a time-varying covariate at the cluster-level. The primary hypothesis will be tested by evaluating the fixed-effect odds ratio for patient receipt of comprehensive testing prior to 1L therapy (after adjustment for time effects).

All analyses will be conducted using Stata (StataCorp, College Station, Texas), or R.

Secondary analyses of primary outcome

Adjustment for demographic and tumor related factors. We will rerun the primary outcome logistic model adjusting for baseline demographic variables (age, sex, smoking status, performance status, insurance type). We will marginalize over coefficient estimates to obtain marginal risk difference and ratio estimates and respective 95% confidence intervals.

Secondary Outcomes

Secondary outcomes include: 1) successful EHR based nudge delivery, 2) turnaround time of delivery of provider focused alerts after receipt of plasma genotyping results, 3) completion of comprehensive molecular testing (tissue and/or plasma testing), 4) reasons for failure to complete comprehensive molecular testing (QNS or other), 5) time to molecularly-informed treatment initiation, 6) type of therapy received (targeted therapy, chemo-immunotherapy, immunotherapy, clinical trial or none) and 7) overall survival at 1 year, and 2 years.

Analysis of secondary outcomes

Analyses of continuous, binary, and time to event outcomes will use linear, logistic, and Cox proportional hazards regression, respectively. Standard model diagnostics will be used to check model assumptions (e.g. proportional hazards). Models will include the randomized intervention. Covariate-adjusted and per protocol analyses will also be run for secondary outcomes.

Statistical Power and Sample Size

Sample Size

Objective 1: We have calculated sample size based on estimates of completion of comprehensive molecular testing prior to initiation of first line therapy. Based on our prior studies, we anticipate that the baseline rate of comprehensive molecular testing prior to first line therapy is 60%. In this stepped wedge cluster randomized trial, we wish to detect an absolute increase of 20% in our primary outcome for patients in the intervention arm.

A sample of 3 clusters in a complete stepped-wedge cluster-randomized design with 4 time periods (including the baseline), 3 steps, 1 cluster(s) switching from control to treatment at each step, and an average of 120 subjects per cluster with an average of 30 subjects per cluster per time period (for a total sample size of 360 subjects) achieves 80% power to detect a difference between proportions of 0.21701. The treatment proportion is assumed to be 0.81701 under the alternative hypothesis. The control proportion is 0.6. The test statistic used is the two-sided Wald Z-Test. The assumed ICC is 0, but is subject to change slightly, and the test will be conducted with a 5% type-1 error.

Objective 2: Proposed sample size is based on the estimated number of interviews needed to reach data saturation within each group and by intervention outcome to support mixed methods evaluation; however, interviews will continue until saturation is achieved.

Approach to missing data

Missing data can contribute to bias and inefficiency in trial analysis. We are not expecting missing primary outcome data because the data are extracted from EHR. We do anticipate that there may be some missing data among covariates used for adjustment, and in secondary outcomes, mostly due to failure to enter data by the doctors and medical staff. To ensure that data are as complete as possible, we will return to charts as often as needed. After that, missingness may be addressed by methods at analysis time.

The primary analysis of testing completion will be presumed to be using complete data, and use only the structural trial measures, including treatment (active nudge versus control), time, and step or cluster id. The secondary analysis of testing completion will include covariates. We will first do a complete data only analysis. This will be followed by and compared to a multiple imputation analysis to test the sensitivity of regression coefficients to missingness. We will use the same approach with multiple imputation and sensitivity analysis to the secondary outcomes.

Safety data and interim analysis

Trial stopping rules / safety monitoring measures

We do not plan to monitor for safety. It is not a medical intervention, and we have the appropriate waiver from the IRB.

Interim analysis

No interim analysis is planned.

Timing of final analysis

Final analysis will occur following completion of the intervention on June 15, 2025 through May 2026.

Person performing analysis

Statistical analysis will be performed by the trial's statistical team.

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