WF 01414: Improving Resection Rates among African Americans with NSCLC (“Southern Lung Cancer Study”)

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Study Design: This is a two-arm, stratified cluster-randomized, cancer care delivery trial to determine if an enhanced, protocol-driven, patient navigation (EPDPN) intervention will improve rates of lung-directed therapy with curative intent (LDTCI; defined as surgical resection or stereotactic body radiotherapy [SBRT]) in African Americans (AAs) in the southern United States (US) with recently diagnosed, probable/proven, early stage non-small cell lung cancer (NSCLC) versus usual care.

Study Sample: 200 (100 patients per arm) AA patients with recently diagnosed, probable/proven, early stage NSCLC evaluated/treated at eligible sites in the southern US.

Study Duration: Each participant will be followed for 13 months post enrollment. Vital status will be tracked until death or end of the study period, whichever occurs first.
Study Site
Eligibility Criteria:

INCLUSION CRITERIA
1. Located in a southern US state according to the US Census Bureau:
   - South Atlantic US: Delaware, Maryland, Washington DC, West Virginia, Virginia, North Carolina, South Carolina, Georgia, Florida.
   - East South Central US: Kentucky, Tennessee, Mississippi, Alabama.
   - West South Central US: Oklahoma, Arkansas, Louisiana, and Texas.
2. On average, cared for at least 3 AA patients with early stage NSCLC per year (based on the last 3 years of the site’s cancer registry data).
3. Has a study site-specific nurse available to act as a patient navigator (PN) or has a (study site-specific or shared) nurse available to act as a “clinical consultant” to a study site-specific, non-nurse navigator.

Participant Eligibility Criteria:

INCLUSION CRITERIA
1. Age 21 years or older.
2. AA or Black race.
3. Recently diagnosed (i.e., within 70 days of enrollment) with clinically suspicious or biopsy-proven (“probable/proven”), early stage (i.e., stage I-II) NSCLC.
4. Evaluated/treated for probable/proven NSCLC at an eligible study site (see above).
5. Ability to understand written and/or spoken English.
6. Access to a telephone.
7. Ability to understand and willingness to sign an informed consent document.

EXCLUSION CRITERIA
1. Status post-surgical resection or SBRT for recently diagnosed, probable/proven, early stage NSCLC.
2. Locally advanced (Stage IIIA-IIIB) or metastatic (stage IV) NSCLC.
3. Previous history of lung cancer.
4. Diagnosis of any other invasive cancer that requires ongoing treatment or for which there is evidence of active disease (other than non-melanoma skin cancer or carcinoma in situ of the cervix).
5. Currently in hospice care.
INDEX

COVER PAGE.........................................................................................................................2

SCHEMA...............................................................................................................................3

1. OBJECTIVES....................................................................................................................6

2. BACKGROUND...................................................................................................................7

3. SUMMARY OF STUDY PLAN..........................................................................................14

4. STUDY SITE AND PARTICIPANT SELECTION...............................................................19

5. AGENT ADMINISTRATION .............................................................................................NA

6. PHARMACEUTICAL INFORMATION .............................................................................NA

7. CLINICAL EVALUATIONS AND PROCEDURES...........................................................26

8. PROTOCOL SPECIFIC TRAINING REQUIREMENTS.......................................................34

9. SPECIMEN MANAGEMENT ..........................................................................................NA

10. REPORTABLE ADVERSE EVENTS/SEVERE ADVERSE EVENTS........................................34

11. STUDY MONITORING ..................................................................................................35

12. STATISTICAL CONSIDERATIONS................................................................................37

13. PROTECTION OF HUMAN SUBJECTS.........................................................................41

REFERENCES .......................................................................................................................45

Appendix A Letter To Referring Physicians

Appendix B Recruitment Flyer: Southern Lung Cancer Study
Appendix C Pre-Screener
Appendix D Eligibility Screener
Appendix E Registration Form

Appendix F Usual Care Group Packet:
Frequently Asked Questions
Participant Survey Answer Guide
Study Participant Telephone Survey Calendar

Appendix G Intervention Group Packet:
Frequently Asked Questions
Participant Survey Answer Guide
Study Participant Telephone Survey Calendar

MUSC Staff Use Only

Appendix H Baseline & Follow-Up Survey

Appendix I Periodic Assessment of Treatment and Vital/Disease Status
1. OBJECTIVES

The goal of this 5-year R01 study is to improve rates of lung-directed therapy with curative intent (LDTCI) in African Americans (AAs) in the southern United States (US) with recently diagnosed (i.e., within 70 days of study enrollment), clinically suspicious or biopsy-proven (i.e., “probable/proven”), early stage (stage I-II), non-small cell lung cancer (NSCLC) via an enhanced, protocol-driven, patient navigation (EPDPN) intervention. Lung resection is the standard-of-care in medically fit patients with early stage lung cancer, and multiple studies have shown that improvements in lung resection rates translate into improvements in overall survival. AAs with early stage NSCLC are significantly less likely than European Americans (EAs) to undergo lung resection. Recently, stereotactic body radiation therapy (SBRT) has been established as an alternative mode of LDTCI in patients with biopsy-proven, early stage NSCLC who are deemed medically ineligible for surgical resection (due to limited pulmonary reserve, significant/active co-morbidities, frailty, etc.).

The organizing hypothesis of the proposed work is that an EPDPN intervention aimed at reducing potential barriers to care will improve rates of LDTCI among AA patients with recently diagnosed, probable/proven, early stage NSCLC.

Previous quantitative and qualitative studies with AA patients have investigated the role of sociodemographic and tumor factors on racial disparities in surgical therapy for NSCLC. These findings have been incorporated into a novel EPDPN intervention designed for patients with recently diagnosed, probable/proven, early stage NSCLC. We will test the intervention in a two-arm, stratified cluster-randomized, cancer care delivery trial comparing the intervention versus usual care. Study participants will be recruited from study sites across the southern US, including the Medical University of South Carolina Hollings Cancer (MUSC HCC) and the Comprehensive Cancer Center of Wake Forest NCORP Research Base (WF NCORP RB) and its affiliated sites. Participants will be randomized by study site.

1.1. Primary Objectives

1.1.1. To evaluate the impact of an EPDPN intervention on rates of LDTCI in AAs in the southern US with recently diagnosed, probable/proven, early stage NSCLC.
1.1.2. To evaluate the modifying effects of income on the relationships between the intervention and rates of LDTCI.
1.1.3. To evaluate the modifying effects of urban-rural residence on the relationships between the intervention and rates of LDTCI.

Primary hypotheses

- Participants in the intervention group will have higher rates of LDTCI than participants in the usual care group.
- The increase in receipt of LDTCI in the intervention group (compared to the usual care group) will be greater in participants with low income than in those with moderate-to-high income.
- The increase in receipt of LDTCI in the intervention group (compared to the usual care group) will be greater in participants from rural areas than in those from urban areas.
1.2. Secondary Objectives

1.2.1. To evaluate the impact of an EPDPN intervention on rates of surgical and/or radiation oncology consultation.
1.2.2. To evaluate the impact of an EPDPN intervention on the time to LDTCI.
1.2.3. To evaluate the impact of an EPDPN intervention on satisfaction with care received.
1.2.4. To evaluate the impact of an EPDPN intervention on overall survival.

Secondary hypotheses

- Participants in the intervention group will have higher rates of surgical and/or radiation oncology consultation than participants in the usual care group.
- Participants in the intervention group will have reduced time to LDTCI.
- Participants in the intervention group will have improved satisfaction with care received.
- Participants in the intervention group will have improved overall survival.

1.3. Tertiary Objectives

1.3.1. To evaluate the impact of an EPDPN intervention on barriers to LDTCI, including the belief that exposure to air during surgery causes lung cancer to spread and barriers to care.
1.3.2. To evaluate the impact of an EPDPN intervention on factors mediating patients’ treatment decisions (Figure 2.2.10).

Tertiary hypotheses

- Participants in the intervention group will have lower rates of the belief exposure to air during surgery causes lung cancer and perceived barriers to care than participants in the usual care group.
- Participants in the intervention group will have lower levels of state anxiety and fatalism.
- Participants in the intervention group will have higher levels of health-related quality of life (HRQOL), social support, self-efficacy in communication with health care providers, trust in physicians, and satisfaction with the treatment decision that was made.

2. BACKGROUND

2.1. Study Disease

2.1.1. Burden of Lung Cancer in the US and Disproportionate Adverse Impact in AAs

Lung cancer is the leading cause of cancer death in the US. It is estimated that lung and bronchus cancer will account for 224,210 new cancer cases and 159,260 cancer deaths in the US in 2014.\(^1\) AA males have a significantly higher incidence rate and are twice as likely to die from lung and bronchus cancer compared to EA males.\(^1\) Approximately one-third of patients with NSCLC (the most common type of lung cancer) present with early stage, potentially curable disease. Although AAs are only slightly less likely to present with localized disease compared to EAs (37% versus 40%), their overall 5-year survival is significantly lower (45% versus 54%).\(^1\) Of note, median survival time for patients with localized disease has been consistently lower for AAs compared to EAs between 1996-2005: 26.0 months versus 38.5 months.\(^2\)
2.1.2. Surgery Is the Optimal Treatment for Patients with Early Stage NSCLC

Surgery (i.e., lung resection) is the standard-of-care for otherwise medically fit patients with probable/proven, early stage, NSCLC. Current evidence suggests that surgical resection (i.e. wedge resection, lobectomy, or pneumonectomy) is associated with improved survival and is the most effective therapeutic option. The combined 5-year survival of resected patients with Stage I or II NSCLC is about 40%. In contrast, the median survival of patients who are not resected is less than one year.

2.1.3. AA Race Adversely Impacts Receipt of Surgical Therapy for Early Stage NSCLC

Several studies have reported significantly lower rates of surgical resection among AAs with NSCLC, even when controlling for stage at presentation. Bach et al. used 1985-93 SEER-Medicare data from Stages I-II NSCLC patients to compare surgical resection and survival rates between 10,984 EAs and AAs. The rate of surgery in AAs was only 64.0%, compared to 76.7% among EAs (p<0.001). AA race was associated with a relative risk of resection of 0.54, even when controlling for the effects of age, gender, comorbidity, median income, and tumor stage. Five-year survival was lower for AAs compared to EAs (26.4% versus 34.1%, p<0.001). In contrast, the five-year survival of AA and EA patients who underwent surgery was roughly similar (39.1 v. 42.9%, p=0.10), as was survival among patients who did not undergo surgery (4% v. 5%, p=0.25). The racial disparity in resection rates largely accounted for the lower survival rate among AAs. In a more recent study, Hardy et al. conducted an evaluation of the likelihood of resection in a SEER-Medicare based sample of 83,101 AA (n=7,960, 9.6%) and EA (n=75,141, 90.4%) patients ages 65 years and older with Stages I-IV NSCLC. In patients with Stages I-II NSCLC, AAs were 37% less likely (OR, 0.63, 95% CI 0.55-0.73) to receive surgery.

The independent effect of AA race on use of surgical resection in patients with NSCLC in South Carolina (SC) was recently analyzed by the investigators. All cases of non-metastatic, resectable NSCLC reported to the SC Central Cancer Registry between 1996-2002 were identified and linked to the state Inpatient Files and Outpatient Surgery Files and the 2000 Census by the SC Office of Research and Statistics. Comorbidity (Deyo-Charlson Index) was calculated using ICD-9-CM codes. Educational level and income were estimated at the zip code level using Census data. Characteristics between EA (n=2,506) and AA (n=550) patients were compared using chi-square tests. The odds ratios (ORs) of resection and 95% CI were calculated using logistic regression. AA patients were more likely to be younger, male, non-married, less educated, poor, uninsured/covered by Medicaid (all p<0.0001), and to reside in rural communities (p=0.0005). AA patients were less likely to undergo curative resection compared to EA patients (44.7% v. 63.4%, P<.0001; unadjusted OR, 0.46; 95% CI, 0.39-0.56). To determine the independent effect of race on the odds of resection while controlling for the other patient- and tumor-related variables, sequential multivariate models

<table>
<thead>
<tr>
<th>Models</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Race (African American vs. Caucasian)</td>
<td>0.46 (0.39-0.56)</td>
</tr>
<tr>
<td>2. Model 1 + Demographics*</td>
<td>0.45 (0.36-0.55)</td>
</tr>
<tr>
<td>3. Model 2 + Comorbidity</td>
<td>0.42 (0.34-0.53)</td>
</tr>
<tr>
<td>4. Model 3 + SES*</td>
<td>0.46 (0.36-0.58)</td>
</tr>
<tr>
<td>5. Model 4 + Tumor factors*</td>
<td>0.43 (0.34-0.55)</td>
</tr>
</tbody>
</table>

*Age, gender, marital status; *Roman-Charlson Comorbidity Index; *Socioeconomic Status: patient residence, income, education, insurance status; *Tumor location, year of diagnosis

8
were created (Table 2.1.3). Based on the results of this population-based and racially diverse study, the investigators concluded that AA race was a powerful, independent predictor of underuse of surgical resection among AA patients with non-metastatic NSCLC in SC, even when controlling for age, comorbidity, income, and insurance status.

Lathan et al. analyzed the effect of race on invasive staging and surgery in 21,219 patients with Stages I-III NSCLC using SEER-Medicare data and found that AA patients were less likely to undergo invasive staging compared to EA patients (OR 0.75; 95% CI, 0.67-0.83). To control for differences in access to care, the investigators also analyzed the effect of race on the likelihood of surgery among staged patients. AA race was a powerful, negative predictor of surgical resection (OR, 0.55; 95%CI 0.47-0.64), even when the analysis was limited to patients previously staged with mediastinoscopy (i.e., patients who had been evaluated by a surgeon and undergone an invasive staging procedure). In addition, AA patients were more likely to refuse surgery (3.4% versus 2.0%, p=0.013).

If AA patients with early stage NSCLC received surgical resection at the same rate as EAs, their percent discrepancy in 5-year survival would be only 3.3 percent. In this health disparities-focused proposal, we will focus our intervention on AAs because they bear a disproportionate burden of the lung cancer mortality in the US. Our intervention is aimed at improving surgical resection rates (and other forms of LDTCl) in AA patients in the southern US with recently diagnosed, probable/proven, early stage NSCLC because, although surgery is the optimal therapy in these patients, it is often underutilized, resulting in racial disparities in cancer survival. A recent analysis of 2000-2011 data from the American College of Surgeons National Cancer Data Base revealed that the average resection rate among AAs with stage I-II NSCLC in the southern US (i.e., “South” region, based on US Census Bureau definitions, see Section 4.1.1) was only 60%. Because there is a paucity of data regarding similar disparities in lung cancer resection rates among other racial/ethnic groups, we have decided to concentrate our efforts on AAs.

2.1.4. Age, Gender, Marital Status, Comorbidity, Urban/Rural Residence, Income, and Insurance Status Impact Receipt of Surgical Therapy for NSCLC

Older patients are less likely to receive invasive procedures than younger patients. Patients ages 70-79 years and 80 years or older are significantly less likely to undergo surgery for NSCLC compared to younger patients, even when controlling for underlying comorbidity.11 Women and separated/divorced or widowed patients are less likely to receive resection for NSCLC compared to men and married patients, respectively, reflecting their potential lack of social support.9-11 Patients with serious underlying medical conditions are at greater risk for postoperative morbidity and mortality; not surprisingly, greater comorbidity is associated with lower rates of surgical resection.7,11 Patients living in rural areas are less likely to receive cancer surgery compared to urban patients, presumably due to reduced access to surgeons and cancer specialists.11,17,18 Lower income is also associated with underuse of surgical resection for cancer.6,9,10 Work by the investigators demonstrated that living in poverty, Medicaid coverage, and lack of insurance were independent predictors of underuse of surgery in patients with early stage NSCLC.11

2.1.5. Role of Stereotactic Body Radiotherapy (SBRT) in the Treatment of Patients with Biopsy-Proven, Early Stage NSCLC
Recently, SBRT has been established as an alternative mode of LDTCI in patients with biopsy-proven, early stage NSCLC who are deemed medically ineligible for surgical resection (due to limited pulmonary reserve, significant/active co-morbidities, frailty, etc). SBRT is a treatment procedure similar to central nervous system (CNS) stereotactic radiosurgery, except that it deals with tumors outside of the CNS. A stereotactic radiation treatment for the body means that a specially designed coordinate-system is used for the exact localization of the tumors in the body in order to treat it with limited but highly precise treatment fields. SBRT involves the delivery of a single high dose radiation treatment or a few fractionated radiation treatments (usually up to 5 treatments). Patients are evaluated for SBRT by radiation oncologists, who plan and administer the treatments.

2.2. Study Intervention

2.2.1. Description of Patient Navigation

Patient navigation interventions are an emerging approach to reducing cancer disparities. Dr. Harold P. Freeman created one of the first patient navigation programs in 1990 to help women navigate the process of breast cancer screening and follow-up care. Patient navigation is based on social support theory and is an evidence-based, barrier-focused intervention designed to ensure timely and efficient access to needed health services. Navigators focus on case identification, identify barriers to care, and implement a care plan. Psychosocial interventions such as patient navigation are effective in addressing many of the psychosocial and practical barriers to care facing patients who are newly diagnosed with cancer. Lack of access to specialty care is a particular problem for AAs. Dynamic patient navigation interventions reduce individual, sociocultural, economic, and organizational barriers to care.

2.2.2. Effectiveness of Prior Patient Navigation Programs

The NCI recently funded several sites to conduct and evaluate patient navigation interventions to promote cancer screening and treatment adherence. Wells et al conducted a review of 45 articles in the PubMed database that focused on patient navigation interventions, 16 of which provided data on the efficacy of navigation in improving timeliness and receipt of cancer screening, diagnostic follow-up care, and treatment. The reported increases in adherence to diagnostic follow-up care in the navigated patients ranged from 21% to 29.2% compared to control patients. Ell et al recently conducted a randomized trial of a navigation intervention to improve rates of follow-up of abnormal mammograms in a sample of 204 low income, ethnic minority women. The intervention group was much more likely to be adherent through diagnostic resolution than the control group (90% vs. 66%, OR=4.48, p<0.001) and was more likely to experience timely treatment than the usual care group (77% vs. 57%, OR=2.5, p=0.01). In a recent study, Battaglia et al conducted a patient navigation intervention to improve follow-up of abnormal breast cancer screening in an urban population. In the sample of 1,332 patients (40% of whom were AA and 68% of whom had either public insurance or no insurance), women in the intervention group had 39% greater odds of having timely follow-up (95% CI, 1.01-1.9). Timely follow-up was associated with older age (p=0.0003) and having private insurance (p=0.006). In summary, prior studies show that breast cancer navigation interventions improve timeliness and receipt of treatment.

2.2.3. LDTCI for NSCLC is an Excellent Extension of the Patient Navigation Model
To date, patient navigation interventions have been conducted primarily in women with breast cancer to optimize rates of screening, diagnosis and treatment. In contrast, lung cancer is a disease in which men bear a heavy burden. Men may require different types of navigation activities and intensities compared to women. This trial will include both women and men and will therefore bring light to bear on this issue. Moreover, unlike cancer screening, LDTCI can be associated with significant morbidity and mortality. It is important to examine whether an EPDPN intervention can reduce the barriers impacting the deeply personal set of decisions and actions on which patient decision making is often based.

The investigators of this trial recently completed a qualitative study of factors affecting patients’ potential willingness to undergo surgical resection for NSCLC and perceptions of PNs among subjects "at risk" for lung cancer. Four focus groups (2 with AAs and 2 with EAs) with patients "at risk" for NSCLC were conducted to explore their potential willingness to undergo resection for lung cancer and to assess their perceptions of a possible patient navigation intervention to improve receipt of surgical resection. Among AAs, willingness to undergo resection was negatively associated with: reported fear of cancer and its treatment, a widely held belief that exposing cancer to air during surgery causes the cancer to spread (“once they open you up, all it [cancer] does is spread to the rest of the body”), mistrust of surgeons (“doctors just want to cut you”), and mistrust of the health care system. AAs stated a desire to receive the following from a PN: medical information (“good information and direction”), information about the risks and benefits of lung cancer surgery and alternative treatments (“being walked through the treatment process”), access to testimonials from patients who had successfully undergone surgical resection for lung cancer, help with financial barriers to surgery (e.g., transportation barriers), and emotional support during the decision-making process (“receiving comfort would be helpful”). AA participants unanimously expressed interest in working with a PN to meet these needs.

2.2.4. Patient Navigators (PNs) Can Reduce the Impact of Individual Barriers on Receipt of LDTCI

Individual barriers include patients’ misconceptions about cancer and its treatment that may contribute to their willingness to undergo LDTCI. Margolis et al interviewed 626 patients (61% of whom were AA) in pulmonary/lung cancer clinics in Philadelphia, Los Angeles, and Charleston to assess the prevalence of the belief that exposure to air during lung surgery causes cancer spread and its influence on potential willingness to have lung cancer surgery. Thirty-eight percent of patients stated that they believed that air exposure at surgery caused tumor spread. In multivariate analysis, the most significant predictor of this belief was AA race (OR, 3.5; 95% CI, 1.9 to 6.5). Of note, 19% of AA patients stated that this belief was a reason for avoiding surgery, and 14% stated that they would not accept their physicians’ reassurance that the belief was false.

Higher risk aversion to surgery may partly account for the apparent underuse of surgical treatment among AA patients. In a prospective study of 708 EA and AA patients with carotid stenosis facing the prospect of carotid endarterectomy, Bosworth et al found that increased age, AA race, no previous surgery, lower level of chance locus of control, less trust of physicians, and less social support were independently associated with greater risk aversion to surgery.

PNs can reduce misconceptions by correcting medical misinformation and emphasizing the importance of LDTCI in patients with probable/proven, early stage NSCLC while
acknowledging patients’ fears and concerns. PNs can also provide patients with information, in simple lay language, about treatment options and side effects and can help patients understand that probable/proven, early stage NSCLC should be treated according to national clinical guidelines.

2.2.5. PNs Can Reduce the Impact of Sociocultural Barriers on Receipt of LDTCI

Sociocultural barriers include mistrust, which negatively impacts willingness to undergo LDTCI among AAs. Mistrust of the health care system is related to knowledge of past medical research abuses with AAs. PNs can manage these barriers by developing trusted relationships with patients to overcome their fear and mistrust of LDTCI and/or medical institutions. PNs can also meet patients during their appointments, wait with them until they are seen by a clinician and participate in the clinic appointment if requested to do so by the patient. PNs can arrange for “testimonials” from patients who underwent successful LDTCI for probable/proven NSCLC and can refer patients to social workers and cancer support groups.

2.2.6. PNs Can Reduce the Impact of Economic Barriers on Receipt of LDTCI

The diagnosis and treatment of probable/proven lung cancer is complex and often involves multiple medical tests and consultations with a myriad of medical specialists. Patients with probable/proven NSCLC and limited financial means face unique barriers and economic challenges as they negotiate their way through the medical system. Some of these barriers and challenges include ineligibility for Medicare or Medicaid, lack of health insurance coverage, lack of transportation, and threat of loss of employment due to illness. PNs can address economic barriers by connecting patients with resources and support systems, arranging for financial support, establishing reliable transportation to appointments, and assisting with parking.

2.2.7. PNs Can Reduce the Impact of Organizational Barriers on Receipt of LDTCI

Organizational barriers to cancer treatment include lack of cancer information presented in an understandable way using lay language, lack of coordinated cancer care, and lack of patient appointment reminder systems. Complex bureaucracy in the health care system, poor patient-physician communication, and scheduling difficulties are examples of other organizational barriers that impede positive treatment outcomes. PNs can contend with organizational barriers by providing patients with patient-friendly informational materials about NSCLC, coordinating care among multiple specialists (i.e., pulmonologists, general/thoracic surgeons, radiation and medical oncologists, etc.), linking patients with appropriate follow-up care services and sending patient reminders about appointments with these service areas. PNs can thus reduce doctor-patient communication barriers to LDTCI (before, during, and after surgical and/or radiation oncology consultation).

2.2.8. Effect of EPDPN Intervention on Potential Mediators.

A variety of factors may be impacted by the intervention and may in turn mediate its effect on receipt of LDTCI. Health-related quality of life (HRQOL) is expected to improve following LDTCI because patients will be encouraged by PNs to receive LDTCI. Anxiety is expected to decrease as social support is provided by the PN. The intervention should also positively
impact patients’ feelings of self-efficacy by equipping them to engage in discussions with their clinicians about LDTCI, which could in turn enhance their trust in physicians and increase their satisfaction with their decision to undergo LDTCI.\textsuperscript{43,44}

2.2.9. Proposed Study Intervention

The proposed EPDPN intervention is innovative and has not been tested in this setting. To our knowledge, this is the first study to apply an EPDPN intervention with AA patients with recently diagnosed, probable/proven, early stage NSCLC to improve their receipt of LDTCI. Relative underuse of surgery is an important mediator of racial disparities in cancer survival. The study results will yield important insight into the mechanisms underlying underuse of surgical cancer care (and other forms of LDTCI) in AAs with NSCLC. The results will thus provide a means to optimize care, and in turn, improve survival. The collective partnership of the study sites offers a unique opportunity to test the efficacy of the intervention at a multi-institutional, regional-level.

2.2.10. Conceptual Framework of the Hypothesized Relationships

Sociodemographic characteristics (moderators) impact the experience of individual, sociocultural, economic, and organizational barriers to surgical resection.\textsuperscript{39} We hypothesize that the EPDPN intervention will reduce potential barriers to LDTCI, improve mediating psychosocial outcomes, and increase rates of LDTCI in AAs with probable/proven early stage NSCLC (Figure 2.2.10).

Figure 2.2.10 Hypothesized Relationships among the Study Variables

2.3. Rationale

This trial is significant for many reasons. First, it has important implications for optimizing cancer care for AA adults from diverse age and socioeconomic strata. Second, this trial extends the patient navigation model to the area of LDTCI; most published literature related to patient navigation is focused on cancer screening. Third, the innovative use of patient navigation in this study will add considerably to existing knowledge regarding the potential impact of patient navigation on males, patients with probable/proven lung cancer, and patients facing LDTCI.
Fourth, to our knowledge, no previous randomized trials of patient navigation interventions in AAs with newly diagnosed, probable/proven, early stage NSCLC exist. As such, this trial will advance the navigation model by testing it in an understudied area (i.e., to increase receipt of LDTCI for probable/proven lung cancer). Fifth, the results of the trial will shed light on the influence of income and urban/rural residence on the study outcomes, thus allowing us to expand the conceptual framework of factors associated with surgical resection (and other forms of LDTCI) for lung cancer.

This trial has high potential impact. First, relative underuse of surgery is an important mediator of racial disparities in survival for many types of cancer; results from this trial may uncover modifiable, root causes underlying disparities in surgical cancer care. Second, while patient navigation interventions have been used extensively in breast cancer screening and treatment, there is no research examining patient navigation in AAs with probable/proven NSCLC; this trial represents an important extension of this model. Third, the potential utility of patient navigation to enhance rates of LDTCI rates among AA patients with probable/proven, early stage NSCLC is an important and understudied area of research. Fourth, evaluation of the patient navigator model to enhance access to LDTCI for AAs with probable/proven NSCLC could lead to significant improvements in care and reductions in racial disparities in cancer outcomes. The application of this intervention in this clinical arena is novel. If the intervention is successful, it will be an important tool available for use by other health care institutions and states.

Our data show that the states with the highest rates of underuse of surgical resection for early-stage NSCLC are located in the southern US. As such, we have explicitly chosen to focus our study and recruitment efforts on the states that could gain the most benefit from their study participation. A later study could compare outcomes in southern vs. northern states to identify whether the impact of the navigation intervention is moderated by geographic differences in access to care, perceived discrimination, mistrust of the health care system, etc.

3. SUMMARY OF STUDY PLAN
3.1. Overview of Research Program and Focus of Proposed Study

We will test a novel EPDPN intervention designed to reduce individual, sociocultural, economic, and organizational barriers to LDTCI in 200 AAs in the southern US with recently
diagnosed, probable/proven, early stage NSCLC with the aim of increasing rates of LDTCI in this at-risk population.

3.2. Conduct of the Randomized Trial

3.2.1. Study Design

Two-arm, stratified cluster-randomized, cancer care delivery trial to determine if an EPDPN intervention will improve rates of LDTCI in AAs with recently diagnosed, probable/proven, early stage NSCLC in the southern US versus usual care (Figure 3.2.1). Study sites will be stratified by the average number of AAs with stage I-II NSCLC seen per year and randomized to either the intervention study arm or the usual care study arm.

3.2.2. Study Sample

Participants will consist of 200 AA patients with recently diagnosed (i.e., within 70 days of study enrollment), clinically suspicious or biopsy-proven early stage NSCLC.

3.2.3. Study Sites

Study participants will be recruited from eligible study sites (see Section 4.1) throughout the southern US and randomized by study site.

3.2.4. Study Participants

Eligible study participants will be recruited from the above study sites if they meet the inclusion/exclusion criteria outlined in Section 4.2.

3.2.5. Data Acquisition

Appropriate paperwork will be processed for each study site, any participating referring doctor’s offices, and any family member who may aid in necessary study data acquisition to ensure compliance with HIPAA and with IRB requirements. This may include, but is not limited to, off-campus study site forms, medical release forms, and HIPAA waiver forms (which may be embedded in the informed consent forms at some study sites).

Data collected from the medical records may include: date of birth, sex, race, ethnicity, insurance status, social security number, date of probable/proven lung cancer diagnosis, clinical and/or pathologic stage of probable/proven cancer, physician type who made diagnosis, referring physician and referring site, appointment with lung cancer surgeon and/or radiation oncologist, type of cancer treatment planned (and ultimately received), dates of cancer treatments (including LDTCI), comorbidity, date of death (if applicable), and other information that is necessary for the study. The social security number will be necessary to assess vital status through the National Death Index for patients lost to follow-up and/or for whom vital status information is not available in the cancer registries. We may also review outpatient records and emergency department records, including initial history and physicals and follow-up notes, radiology reports, and laboratory/pathology reports.

3.2.6 MUSC and WF
Participants will be recruited at Research Base sites and registered through the WF CCRBIS system. Participants will be followed by individual sites. Data will be collected by MUSC.

3.3. Patient Outcome Measures

3.3.1. Primary Outcome

Receipt of LDTCI. This outcome will be assessed via periodic assessments of treatment by MUSC study staff and confirmed by medical record reviews conducted by the study site coordinator (SSC) at the usual care sites or the Patient Navigator (PN) at the EPDPN intervention sites. Receipt of LDTCI will be defined as lung resection (as defined by descriptions and/or billing codes listed in the table below) or SBRT (as defined by the description and/or billing codes listed in the table below) with curative intent within 4 months following diagnosis of probable/proven NSCLC.

Healthcare Common Procedure Coding System (HCPCS) and International Classification of Diseases (9th revision; ICD-9) procedure codes for LDTCI

<table>
<thead>
<tr>
<th>Type of LDTCI</th>
<th>HCPCS procedure codes</th>
<th>International Classification of Diseases (9th revision; ICD-9) procedure codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wedge resection (open)</td>
<td>32484, 32500</td>
<td>32.29, 32.39</td>
</tr>
<tr>
<td>Wedge resection (VATS; video-assisted thoracoscopic surgery)</td>
<td>32666, 32667, 32668</td>
<td>32.20, 32.30</td>
</tr>
<tr>
<td>Lobectomy (open)</td>
<td>32480, 32482, 32486</td>
<td>32.40, 32.49</td>
</tr>
<tr>
<td>Lobectomy (VATS)</td>
<td>32663</td>
<td>32.41</td>
</tr>
<tr>
<td>Pneumonectomy (open)</td>
<td>32440, 32442, 32445, 32488</td>
<td>32.5, 32.59</td>
</tr>
<tr>
<td>Pneumonectomy (VATS)</td>
<td>32.50</td>
<td></td>
</tr>
<tr>
<td>Radical resection of thoracic structures</td>
<td></td>
<td>32.6</td>
</tr>
<tr>
<td>SBRT (delivered in a total 1-5 sessions [fractions])</td>
<td>G0251, G0339, G0340, 77373, 77435</td>
<td></td>
</tr>
</tbody>
</table>

3.3.2. Secondary Outcomes

- Receipt of surgical and/or radiation oncology consultation (defined as outpatient or inpatient consultation with a general or cardiothoracic surgeon and/or radiation oncologist to discuss LDTCI for NSCLC within 4 months post-diagnosis of probable/proven, early stage NSCLC),
- Time to LDTCI (in patients who underwent LDTCI only; defined as the length of time from date of initial diagnosis of probable/proven, early stage NSCLC to date of LDTCI during the 12 months post-enrollment), and
- Time to death (defined as the length of time from date of initial diagnosis of probable/proven, early stage NSCLC to date of death from any cause during entire study period) will be assessed via periodic assessments of treatment by MUSC HCC study staff and confirmed by medical record reviews conducted by the SSCs/PNs at each site.
study site. In patients who are lost to follow-up (with respect to time to death), the cancer registries at each site and the Social Security Death Index will be queried.

- Satisfaction with care received will be assessed via telephone survey administered by MUSC HCC study staff at 6 months post-enrollment.

### 3.3.3. Tertiary Outcomes

We will collect data on potential individual barriers to receipt of LDTCI, moderators that may modulate the effect of these barriers, and mediators of the main study outcomes (Figure 2.2.10 and Table 3.3)

#### 3.3.3.1. Barriers to Receipt of LDTCI

Potential individual barriers to receipt of LDTCI include the belief that exposure to air during lung surgery causes cancer to spread and barriers to care. Belief that exposure to air during lung surgery causes cancer to spread will be measured using one item developed by Margolis et al. Barriers to care will be measured using an instrument based on the National Cancer Institute-funded Navigation Program.

#### 3.3.3.2. Moderators of Interest

The moderators of primary interest are income and urban-rural status. Income level (and household size) will be measured using a demographic item from the National Health and Nutrition Examination Survey. Low income will be defined as an annual household income less than 1.5 times the national poverty level, adjusted for household size, and moderate to high income level will be defined as an annual household income greater than or equal to 1.5 times the poverty level, adjusted for household size. Other moderators of interest (age, gender, ethnicity, marital status, educational level, and insurance status will also be assessed using demographic items from the National Health and Nutrition Examination Survey. Underlying comorbidity, which may affect surgeons’ willingness to recommend and participants’ willingness to undergo surgical resection, will be measured using a survey based on the Romano-Charlson Comorbidity Index, and subsequently confirmed by the SSCs/PNs at baseline via medical record reviews. Tobacco use (i.e., smoking status) will be measured using two items from the Behavioral Risk Factor Surveillance System Survey Questionnaire. Risk attitude, a personality attribute, will be assessed using a 3-item measure developed by Ayanian and Epstein. Faith will be measured using the Santa Clara Strength of Religious Faith Scale Brief.

### Table 3.3 Measurement Instruments and Assessment Time Points

<table>
<thead>
<tr>
<th>Concept Being Measured</th>
<th>Name of Measurement Instrument</th>
<th>Data Collection Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>BARRIERS TO LDTCI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belief that exposure to air during lung surgery causes cancer to spread</td>
<td>Item developed by Margolis et al</td>
<td>Baseline, 3, 6, and 12 months post-enrollment</td>
</tr>
<tr>
<td>Barriers to care</td>
<td>Investigator-developed instrument (20 items) Based on Dr. Elizabeth Calhoun’s NIH/NCI funded Patient Navigation Program</td>
<td>Baseline, 3, 6, and 12 months post-enrollment</td>
</tr>
<tr>
<td>MODERATORS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sociodemographic characteristics (age, gender, ethnicity, marital status, educational level, income level, and insurance status)</td>
<td>National Health and Nutrition Examination Survey, US Census[^58], Behavioral Risk Factor Surveillance System Survey Questionnaire[^59], National Survey of Black Americans[^60] (7 items)</td>
<td>Baseline</td>
</tr>
<tr>
<td>------</td>
<td>---------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Comorbidity Index[^61]</td>
<td></td>
</tr>
<tr>
<td>Tobacco use (smoking status)</td>
<td>Tobacco Use Measure[^7] (2 items)</td>
<td></td>
</tr>
<tr>
<td>Urban-rural status</td>
<td>U.S. Census, based on census tract/zip code[^62]</td>
<td></td>
</tr>
<tr>
<td>Risk attitude</td>
<td>Developed by Ayanian and Epstein[^63] (3 items)</td>
<td></td>
</tr>
<tr>
<td>Faith</td>
<td>Santa Clara Strength of Religious Faith Scale Brief[^53,54] (5 items)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Function</td>
<td>Results of pulmonary function testing</td>
<td>Medical record reviews at 5 and/or 13 months</td>
</tr>
<tr>
<td><strong>MEDIATORS</strong></td>
<td><strong>Baseline, 3, 6, and 12 months post-enrollment</strong></td>
<td></td>
</tr>
<tr>
<td>HRQOL</td>
<td>VR-12[^47,48] (14 items)</td>
<td></td>
</tr>
<tr>
<td>State anxiety</td>
<td>PROMIS[^55] (7 items)</td>
<td></td>
</tr>
<tr>
<td>Fatalism</td>
<td>Fatalism Scale[^61] (5 items)</td>
<td></td>
</tr>
<tr>
<td>Social support</td>
<td>ISEL-12[^61] (12 items)</td>
<td></td>
</tr>
<tr>
<td>Self efficacy in communication with health care providers</td>
<td>Communication and Attitudinal Self-Efficacy (CASE-Cancer)[^64] (12 items)</td>
<td></td>
</tr>
<tr>
<td>Trust in physician</td>
<td>Trust in Physician[^65,66] (11 items)</td>
<td></td>
</tr>
<tr>
<td>Intention to undergo LDTCI</td>
<td>Modification of item developed by Myers et al[^67]</td>
<td></td>
</tr>
<tr>
<td>Satisfaction with treatment decision that was made</td>
<td>Satisfaction with Decision Scale[^68] (6 items)</td>
<td>3, 6, and 12 months post-enrollment</td>
</tr>
<tr>
<td><strong>PRIMARY OUTCOME</strong></td>
<td><strong>Baseline</strong></td>
<td></td>
</tr>
<tr>
<td>Receipt of LDTCI</td>
<td>Inquiry at time of periodic assessments</td>
<td>3, 6, 9, and 12 months post-enrollment (confirmed by medical record reviews at 5 and 13 months)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>SECONDARY OUTCOME</strong></th>
<th><strong>3, 6, 9, and 12 months post-enrollment (confirmed by medical record reviews at 5 and 13 months)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Receipt of surgical and/or radiation oncology consultation</td>
<td>Inquiry at time of periodic assessments</td>
</tr>
<tr>
<td>Time to LDTCI (patients who received LDTCI only)</td>
<td>Inquiry at time of periodic assessments</td>
</tr>
<tr>
<td>Satisfaction with care received</td>
<td>Patient Satisfaction[^69] (28 items)</td>
</tr>
<tr>
<td>Time to death</td>
<td>Inquiry at time of periodic assessments</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>OTHER MEASURES</strong></th>
<th><strong>Satisfaction with Patient Navigation Services (investigator-developed) (9 items)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Periodic assessment of treatment(s) received and vital/disease status</td>
<td>Survey developed for this study</td>
</tr>
<tr>
<td>Survey of appropriateness/quality of the EPDPN intervention (patients in the EPDPN intervention arm only)</td>
<td>6 months</td>
</tr>
</tbody>
</table>

3.3.3.3. Mediators of Treatment Effect

Potential mediators of treatment effect include HRQOL, state anxiety, fatalism, social support, perceived self-efficacy in patient-physician interactions, trust in physician, intention to undergo
LDTCI, and satisfaction with treatment decision that was made. The psychometric properties of the measures used to assess these mediators are robust in AA populations. Intention to undergo LDTCI will be assessed using a one-item measure based on an instrument developed by Myers et al.\(^6\)

### 3.4. Data Collection Schedule

Data regarding potential individual barriers to LDTCI, moderators of interest, and mediators of the primary/secondary study outcomes (except for satisfaction with treatment decision made) will be collected from all participants by MUSC HCC study staff at baseline during the initial telephone survey.

MUSC HCC study staff will also conduct follow-up surveys with study participants at 3, 6, 9 and 12 months post-enrollment. The follow-up surveys will collect data regarding the various mediators of interest and the primary/secondary study outcomes. The data collection intervals were chosen to allow time to assess the amount of change in the mediators over time and assess the impact of the intervention on the primary/secondary study outcomes. Data collection intervals were chosen to minimize testing burden among participants while optimizing data capture from patients who do not opt for LDTCI (and who may have significantly shortened/impaired life expectancy).

PNs at the intervention sites will also use data tracking logs to measure type and number of navigation services requested/received by each navigated patient during the intervention period.

SSCs/PNs will conduct an initial medical record review to confirm eligibility prior to enrollment and confirm comorbidities at baseline. In addition, SSCs/PNs will complete a brief form that will require a second medical record review to confirm the primary/secondary endpoints which will occur approximately at 5 months (+/- 15 days). A third and final medical record review to confirm the primary/secondary endpoints will occur at 13 months (+/- 15 days).

### 4. STUDY SITE AND PARTICIPANT SELECTION

#### 4.1. Study Site Eligibility Criteria

Study sites must meet all of the following eligibility criteria.

**4.1.1. Located in a southern US state according to the US Census Bureau**
- South Atlantic US: Delaware, Maryland, Washington DC, West Virginia, Virginia, North Carolina, South Carolina, Georgia, Florida.
- East South Central US: Kentucky, Tennessee, Mississippi, Alabama.
- West South Central US: Oklahoma, Arkansas, Louisiana, and Texas.

**4.1.2. On average, cares for at least 3 AA patients with early stage NSCLC per year (based on the last 3 years of cancer registry data).**

**4.1.3. Has a study site-specific nurse available to act as a PN or has a (study site-specific or shared) nurse available to act as a “clinical consultant” to a study site-specific, non-nurse navigator.**
4.2 Study Participant Eligibility Criteria

4.2.1. Participant Inclusion Criteria

4.2.1.1. Age 21 years or older.

4.2.1.2. African American or Black race.

4.2.1.3. Recently diagnosed \( (i.e., \text{within 70 days of enrollment}) \) with clinically suspicious or biopsy-proven (see Table 4.2.1.3) early stage (\( i.e., \text{stage I-II} \)) NSCLC.

Table 4.2.1.3. International Classification of Diseases for Oncology, Third Edition Codes for Histologic Classification for NSCLC

<table>
<thead>
<tr>
<th>Histologic Classification</th>
<th>Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>8140-7, 8255, 8260, 8310, 8480-1, 8490, 8560, 8570-1</td>
</tr>
<tr>
<td>Bronchioloalveolar carcinoma</td>
<td>8250-4</td>
</tr>
<tr>
<td>Squamous Cell Carcinoma</td>
<td>8070-8, 8050-2</td>
</tr>
<tr>
<td>Large Cell</td>
<td>8012-3, 8022, 8033</td>
</tr>
<tr>
<td>Other/Undifferentiated</td>
<td>All other codes associated with lung primary</td>
</tr>
</tbody>
</table>

4.2.1.4. Evaluated/treated for NSCLC at an eligible study site (see Section 4.1).

4.2.1.5. Ability to understand written and/or spoken English.

4.2.1.6. Access to a telephone.

4.2.1.7. Ability to understand and willingness to sign a written informed consent document.

4.2.2 Participant Exclusion Criteria

4.2.2.1. Status post surgical resection or SBRT for recently diagnosed clinically suspicious or biopsy-proven early stage NSCLC.

4.2.2.2. Locally advanced (Stage IIIA-IIIB) or metastatic (stage IV) NSCLC.

4.2.2.3. Previous history of lung cancer.

4.2.2.4. Diagnosis of any other invasive cancer that requires ongoing treatment or for which there is evidence of active disease (other than non-melanoma skin cancer or carcinoma in situ of the cervix).

4.2.2.5. Currently in hospice care.

4.3. Inclusion of Women and Minorities

4.3.1. Inclusion of Women

NSCLC cancer affects both men and women. Therefore, women will be included in the proposed study. In our previous study using data from the SC Cancer Registry, 66.9% of the AA NSCLC cases were male and 33.1% were female. \(^{11}\) We anticipate a similar ratio of male and female participants in the proposed study.
4.3.1. Inclusion of Minorities

Our intervention is aimed at improving rates of LDTCI (including lung surgery) in AA patients with recently diagnosed, probable/proven, early stage NSCLC. Although surgery is the optimal therapy in surgically fit, early stage, NSCLC patients, it is often underutilized in AAs, resulting in racial disparities in cancer survival. There is a paucity of data regarding disparities in LDTCI (and/or lung surgery) rates among Latinos or other racial/ethnic groups. Therefore, we have decided to concentrate our efforts on AA patients.

4.3.2. Targeted/Planned Enrollment

We will obtain Institutional Review Board (IRB) approval at each study site to conduct the study. The targeted/planned study enrollment by gender, race, and ethnicity is shown below.

<table>
<thead>
<tr>
<th>TARGETED/PLANNED ENROLLMENT FOR THE RANDOMIZED TRIAL OF THE LUNG CANCER PATIENT NAVIGATION INTERVENTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnic Category</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino**</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>Ethnic Category Total of All Subjects*</td>
</tr>
</tbody>
</table>

** Based upon the percentage of Hispanics in SC – Depending on the percentage of subjects ultimately enrolled from other states across the southern US, these figures may be higher.

4.4. Recruitment, Registration, Randomization, and Retention Plan

4.4.1. Recruitment Processes

4.4.1.1. Referral Sources

SSCs/PNs at each study site will generate a list of physicians (from within and/or outside their study site) who have historically referred patients to their study site for diagnostic workup and/or treatment of probable/proven, early stage NSCLC. Examples of potential referring physicians include primary care physicians, radiologists, pulmonologists, pathologists, general surgeons, cardiothoracic surgeons, radiation oncologists and/or medical oncologists.

SSCs/PNs at each study site will contact each referring physician’s office to inform them about the Southern Lung Cancer Study, provide them with their contact information, and
elicit their assistance in identifying potential study participants. They may also mail a letter to each referring physician (or referring physician’s office) to inform them about the Study, provide them with the SSC’s or PN’s contact information, and elicit their assistance in identifying potential study participants (Appendix A). The letter may also be accompanied by a flyer about the Study that can be posted in the referring physician’s work space/office (Appendix B).

4.4.1.2. Identification of Potential Participants

Study sites will take a proactive approach to rapidly identify potential study participants and optimize the study enrollment rate. Potential participants will be identified by the SSCs at the usual care sites or the PNs at the intervention sites. SSCs/PNs will work closely with referring doctor’s offices as well as their facility’s radiologists, pulmonologists, pathologists, general surgeons, cardiothoracic surgeons, radiation oncologists and/or medical oncologists to identify the optimal identification and recruitment processes for their study site.

Depending on each study site’s referral processes, the SSCs/PNs may conduct a weekly review of radiology reports, pathology reports, and clinic schedules/billing records from primary care clinics, pulmonary clinics, general surgery clinics, cardiothoracic surgery clinics, radiation oncology clinics, and/or medical oncology clinics (as well as lung screening programs at each study site). In addition, the SSCs/PNs will participate in lung tumor boards to identify potential participants and to publicize the study among providers (from within and/or outside their study site) who care for these patients and participate in these tumor boards.

4.4.1.3. Eligibility Screening and Recruitment

Once a patient has been identified by a clinician as having probable/proven, early stage NSCLC and has been referred to a study site (and/or one of its affiliated referring physicians), the SSC/PN will complete the Pre-Eligibility Screener, and if the patient is potentially eligible for the study, the SSC/PN will work with the patient’s physician(s) to identify the best time and strategy to meet with each potential participant to:

1) Invite him/her to participate in the study
2) Provide them with a Southern Lung Cancer Study “Frequently Asked Questions” sheet tailored to potential subjects in the Usual Care Group (Appendix F) or the Intervention Group (Appendix G), as appropriate
3) Conduct the Pre-Screener Log (Appendix C)
4) Conduct the Eligibility Screener (Appendix D).
5) Obtain the Informed Consent
6) Provide the participant with a copy of the survey answer guide (Appendix F or G packet)
7) Provide the participant with a copy of the Participant Study Telephone Survey Calendar (Appendix F or G packet)

The standard process for the SSC/PN to administer the Eligibility Screener and informed consent will be in-person, ideally prior to any surgical and/or radiation oncology consultation.

22
If it is not possible to conduct the Screener and informed consent in-person, the SSC/PN will make an introductory telephone call and administer the Eligibility Screener by telephone. If the patient is eligible, the patient will be mailed a packet including:

1) A Southern Lung Cancer Study “Frequently Asked Questions” sheet (Usual Care Group) or Southern Lung Cancer Study “Frequently Asked Questions” sheet (Intervention Group), as appropriate
2) Two copies of the Informed Consent
3) A copy of the survey answer guide
4) A copy of the Participant Study Telephone Survey Calendar

A subsequent review of the medical record of each potentially eligible participant will be conducted by the SSCs/PNs at each study site to ensure that they meet the above inclusion and exclusion criteria.

The SSC/PN may follow-up with the patient to administer informed consent over the phone (if permitted by that study site’s IRB). Documentation of the informed consent obtained over the phone will include one consent document signed by the person obtaining consent and a separate document signed by the participant who was consented. The patient is not considered enrolled until copies of both signed informed consent forms have been received by the study site.

Copies of the informed consents will be given to each participant, the originals will be maintained at each study site, and copies will be sent to MUSC HCC study staff and WF NCORP RB data management via a secure study-specific fax machine (see Section 11.2).

**4.4.1.4. Recruitment Rate**

Previous studies conducted with older adults show recruitment rates of approximately 70%. Previous consent rates with older AAs are in the 65%-70% range. In this intervention study, we estimate a consent rate of 70%. We will attain this consent rate using the following techniques which we have used to successfully recruit and retain AA participants in our previous trials. First, MUSC HCC study staff will contact patients during weekdays, in the evenings and/or on Saturdays. Second, we have chosen telephone administration of the study instruments because this will allow us to stop the surveys, as needed, and call the participants later if they become too fatigued to complete the instruments during a single session. Third, we will give each participant a $50 gift card at each assessment period (i.e., baseline, 3 months, 6 months, and 12 months) in recognition of their time spent in the study.

**4.4.2. Registration Processes**

Registration data must be entered in MUSC RedCap and WF NCORP CCRBIS.

**4.4.2.1 Registration Processes**

MUSC:
Fill out Appendix C, “Pre-Screener Log”, and Appendix D “Eligibility Screener”. Use these forms to complete the on-line registration in REDCap.
REDCap Registration

To login to REDCap, go to <https://redcap.musc.edu>. Enter your MUSC NetID username and password (which may be obtained by contacting Kendrea Knight at knightkd@musc.edu). At the top of the page, click on the “My Projects” tab and then the “NSCLC Navigation Study” database link which will direct you to the study index page. On the left hand side of the screen click on “Add/Edit Records”, you will then chose from the drop-down list beside “Enter a new or existing ID” either “Arm 1: Navigation Arm” or “Arm 2: Control Arm” (depending on which arm your study site has been randomized to). After you have chosen the study arm, you will then provide the participant with a unique screening ID number and hit “Tab” or “Enter”. Fill in the “Pre-Screening Log” and “Eligibility Screener and Informed Consent” forms using the drop down boxes. Please make sure to upload the eligibility screener and signed consents in the appropriate places. If further information is needed, MUSC HCC Program Coordinator will contact you. If unable to upload eligibility and consent in redcap, please fax or mail to:

Attn: Dr. Marvella Ford
Hollings Cancer Center
Medical University of South Carolina
86 Jonathan Lucas St.
MSC 955
Charleston, SC 29425
Fax number 843-876-2573

These forms should be retained in the patient’s research file.

If you have questions related to the MUSC REDCap registration process or require assistance, please contact the MUSC HCC Program Coordinator 8:30am and 5:00pm EST, Monday through Friday at (843) 876-2452 or knightkd@musc.edu.

4.4.2.2 WF NCORP Research Base

All sites must register participants in WF NCORP CCRBIS to receive NCI credit.

A form 310 or IRB letter of approval and an IRB approved consent form must be received by the Research Base Protocol Information Office – Attn: Site Coordinator prior to patient registration. Fax: (336)716-6275

Fill out Appendix E, Eligibility Registration Form’. Use this to complete the on-line registration.

Online Registration

Log on to the WF NCORP RB registration web site at <http://www.phsapps.wfubmc.edu/CCRBIS/Login/defaultlogin.cfm>. Enter your user name and password (which may be obtained by contacting June Fletcher-Steede at jsteede@wfubmc.edu.) In the ‘Patient Registration and Protocol Information’ table, click the ‘Register Patient/Patient Info’, with the corresponding protocol number found in the drop down box to the right. Fill in the eligibility criteria forms using the
If further information is needed by Data Management, they will contact you. Once the patient information has been entered online print a copy of the eligibility checklist/registration form for your records. Press the submit button, a confirmation page will appear. Print this confirmation sheet for your records. The WF NCORP signed consent (as required in protocol) should be faxed or mailed to WF Data Management.

WF NCORP fax number 336-713-6476
Research Base Data Management Center
2000 W 1st Street Suite 101
Winston-Salem, NC 27104

These forms should be retained in the patient’s study file. These forms will be evaluated during an institutional NCI/WF NCORP RB site member audit.

If you have questions related to the registration process or require assistance with registration, please contact the WF NCORP RB DMC between 8:30am and 4:00pm EST, Monday through Friday at (336) 713-3172 or 713-6507.

4.4.3. Randomization Processes

The proposed intervention will be tested in a two-arm, cluster-randomized trial. As such, participants will be randomized by study site (see Section 12.3).

4.4.3.1. Unblinding Methods: N/A

4.4.4. Retention Processes

We estimate a maximum attrition rate of 10% not including participants who may die during the course of the study. To enhance retention of participants in the study, we will employ the following techniques which we have used to successfully recruit and retain AA participants in our previous trials. Nonetheless, we will strive to reduce this attrition rate by employing the following techniques:

- At enrollment, obtaining multiple contact telephone numbers for each participant, including mobile phone numbers
- Employ http://www.theultimates.com as a tracking strategy to locate changed/new telephone numbers and/or addresses of study participants

The recruitment methods described above were successfully used by the investigators in their previous studies recruiting African American adults. Death will be ascertained by vital/disease status assessments at 3, 6, 9, and 12 months, and confirmed by medical record review, inquiry of cancer registries at study sites, and/or inquiry of Social Security Death Index (in patients lost to follow-up).

4.4.4.1 Participant Burden

The burden to participants will be minimized to enhance retention. Patients in the usual care arm receive the current “gold standard” of treatment. The patients in the intervention arm are assigned to a PN, who helps to reduce the barriers to care that could negatively impact the
patients’ receipt of LDTCI. The telephone-administered survey is administered to all study participants at baseline and at 3-, 6-, and 12-months post-enrollment. It takes approximately 30-40 minutes to administer. The telephone mode of survey administration was chosen to reduce the number of visits that would be required by each patient. Interviews are scheduled at the convenience of the study participants. To further reduce burden to the study participants, the interviewers offer breaks during the interview process. Patients in both arms undergo standard therapy visits. Patients in the navigation arm receive standard therapy visits plus the navigation intervention. Outside of the standard therapy visits, no additional clinic visits are required of the study participants.

5. AGENT ADMINISTRATION: N/A

6. PHARMACEUTICAL INFORMATION: N/A

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1. Survey Administration

Once informed consent has been obtained and the informed consent document is received, the SSC/PN will communicate to the MUSC HCC study staff the participant’s contact information and that the participant is ready for baseline survey administration. All the study surveys will be administered by trained MUSC HCC study staff via telephone. A survey answer guide will be provided to the participant either in-person or via mail prior to administration of the baseline survey.

The baseline survey (Appendix H) will collect data about quality of life, anxiety, self-efficacy in communication with health care providers, trust in physician, risk attitude, belief about lung cancer surgery, intention to receive LDTCI, social support, fatalism, faith, perceived barriers to care, comorbidity, tobacco use, and demographics (date of birth, sex, ethnicity, marital status, educational level, household size, income level, employment status, and insurance status).

SSCs/PNs will conduct an initial medical record review to confirm eligibility prior to study enrollment and confirm comorbidities self-reported in the baseline survey.

Subsequent, follow-up surveys (i.e., portions of the baseline survey/Appendix H) will be administered at 3, 6, and 12 months post-enrollment to all participants who are still “on study” at each time point. The follow-up surveys will collect data about quality of life, anxiety, self-efficacy in communication with health care providers, trust in physician, satisfaction with treatment decision made, beliefs about lung cancer surgery, social support, fatalism, perceived barriers to care, satisfaction with care received (assessed only at 6 months), and satisfaction with patient navigation services (assessed only in the intervention group at 6 months).

At 3, 6, 9, and 12 months post-enrollment, MUSC HCC study staff will also administer a brief assessment to obtain information about treatment received and vital/disease status (Appendix I). Participants’ responses will subsequently be confirmed via medical record reviews by the SSCs or PNs at 5 and 13 months post-enrollment.

If registered participants in either study arm are subsequently deemed to be not eligible for
the study (see Sections 4.2 and/or are found not to have early stage NSCLC prior to LDTCI (see Section 7.7 e.g., via lung biopsy), a brief exit interview will be administered at that time point and these patients will be removed from the study and will not be contacted further by study staff.

Patients who opt for hospice care after study registration will remain in the study and be contacted at 3, 6, 9, and 12 months, as outlined above.

7.2. Usual Care Arm

Usual care for patients diagnosed with probable/proven, early-stage NSCLC may include the following: complete staging work-up (e.g., computed tomography [CT] and/or positron emission tomography [PET] scans, possible transbronchial ultrasound [TBUS] or endoscopic ultrasound [EUS], etc), consultation with a general or cardiothoracic surgeon, consultation with a radiation oncologist, consultation with a medical oncologist, cardiac clearance and/or pulmonary function testing (if deemed necessary by the evaluating surgeon), staging mediastinoscopy, surgical resection (wedge resection, lobectomy, or pneumonectomy, as indicated by the size and location of the tumor) or SBRT, and adjuvant therapy (radiotherapy and/or chemotherapy), as medically indicated.

SSCs will not interact with study participants beyond what is considered usual care at each study site (which may or may not include various levels of “patient navigation”), other than to review patients' medical records for study purposes.

7.3. EPDPN Intervention Arm

The proposed Intervention (EPDPN) will be administered by the PNs at the intervention sites on an outpatient basis. Several defining, fundamental characteristics of the PNs will ensure consistency of the intervention delivery across the various study sites. Trained study PNs at each intervention site will be:

• Study site-specific RNs who will be competent to provide the clinical knowledge and support sought by study participants or a study site-specific, non-nurse navigators who will work with a designated (study site-specific or shared) nurse who will serve as their "clinical consultant", and
• Formally trained in the delivery of the intervention to reduce barriers to care that could negatively impact receipt of LDTCI, and
• Established, paid staff familiar with the health care system/resources at each study site.

The PNs will give patients the information they need to make informed decisions about whether to undergo LDTCI. The navigators will also link patients with needed resources to facilitate their receipt of LDTCI. The navigators will not try to convince the patient to have LDTCI. The navigators will go through a formal, standardized training process as described in the protocol. The training will highlight professional boundaries (including informed decision making).

The PN will provide each patient with a copy of the NCI’s “What You Need to Know About Lung Cancer” booklet and encourage them to re-contact his/her primary care physician (or the physician who diagnosed their probable/proven NSCLC) to discuss treatment options.

The PNs will provide patients with their contact information and brief patients on their role. The PNs will navigate study participants for up to 4 months (16 weeks, 112 days) after
NSCLC diagnosis, until the patient is deemed ineligible for LDTCI (i.e., lung resection or SBRT) by their physician(s), until receipt of LDTCI, or death (whichever comes first). If at any point participants go “off treatment” (see Section 7.7), study EPDPN intervention activities will end at that time and usual care will be provided at the discretion of each study site.

During the EPDPN intervention period, PNs will contact each intervention group participant by telephone (or in-person) on weekly basis (at minimum). The role of the patient navigators is to:

(1) help patients who are recently diagnosed with early stage NSCLC schedule clinical appointments;

(2) identify each patient’s unique logistical and emotional needs (barriers to care) and coordinate with professional staff to develop effective solutions;

(3) connect patients to community and social support services;

(4) provide medical appointment reminders;

(5) accompany patients to their clinic appointments as requested;

(6) reschedule appointments when patients cannot keep them;

(7) provide patients with sources of expert information about the recommended surgical treatment;

(8) guide patients through the health care system, including helping them arrive at appointments on time and prepared;

(9) interact with patients to help them resolve financial, language, transportation, or other barriers to treatment;

(10) assist patients in finding ways to pay for their health care by working with financial counselors at the health care site;

(11) organize and coordinate patient transportation services;

(12) provide health education to patients about lung cancer surgery and other relevant information (this may include smoking cessation services);

(13) help patients to access language-specific materials,

(14) facilitate interaction and communication with health care staff and providers;

(15) use lay language to describe the medical terms used by clinicians, and explain patients’ concerns to their health care providers so that these concerns can be addressed;

(16) interact with patients’ specialists to relay patients’ concerns about surgical resection so that they can be addressed by these specialists;
(17) provide support through active, empathic listening;

(18) arrange for patients to hear "testimonials" from other patients with similar racial and ethnic backgrounds who had successful surgical outcomes for treatment of NSCLC

(19) respect patients' medical treatment decisions.

The PNs will also remind participants of the study surveys.

The EPDPN intervention is standardized to ensure consistency of the intervention delivery across the intervention study sites. The navigators employ a secure, web-based data management system, Research Electronic Data Capture (REDCap), to track the frequency, intensity, and content of the EPDPN intervention. Information that is recorded includes the number, length, and type of contact (in-person, telephone, or email) with each participant, and a description of the barriers that were addressed. This system fosters the successful deployment of the intervention in a standardized manner across the intervention sites and it identifies the specific types of barriers to LDTCI that were addressed at each “encounter” through the navigation intervention. The data tracking logs will be used to assess the fidelity of the intervention (see Section 7.8). These data will also be used to estimate the cost (using time-driven, activity-based costing) and cost-effectiveness (increase in quality-adjusted life years/cost) of the EPDPN navigation intervention in a subsequent study.

The navigators will participate in regularly scheduled teleconferences led by the PIs and the MUSC HCC Program Coordinator, during which the intervention will be discussed in detail and training is provided in such areas as developing effective communication approaches, identifying institutional and community resources, and problem-solving.

7.4. Schedule of Events

7.4.1. SSCs or PNs at study sites use only

Data is entered in MUSC RedCap.
Registration is entered in Wake Forest NCORP CCRBIS.

Pre-Baseline
- Administer Pre-Eligibility Screener
- Administer Eligibility Screener

Baseline
- Consent study participant
- Register participant with Wake Forest NCORP CCRBIS to receive your NCI credit (MUSC patient identification number will be needed at registration)
- Fax Consent form to WF Data Management at 336-713-6476 and upload the Consent form in MUSC Redcap.
- Enter participant contact information in RedCap and e-mail the following MUSC HCC study staff immediately:
  - Kendrea Knight (MUSC Study Coordinator) knightkd@musc.edu
• Heidi Varner (MUSC Study Interviewer) varnerh@musc.edu
  “cc”
• Nestor Esnaola (Study MPI) Nestor.Esnaola@fccc.edu
• Marvella Ford (Study MPI) fordmar@musc.edu

To be completed after MUSC staff baseline survey

- First Medical Record Review
- Confirm study eligibility
- Confirm comorbidities (i.e., baseline survey)

7.4.2. Baseline Until Four months After Diagnosis
(Navigation Intervention sites only)

- Contact participants at least weekly and administer study intervention, until deemed not eligible for LDTCI by physician(s), receipt of LDTCI, 4 months (16 weeks, 112 days) after NSCLC diagnosis, or death (whichever occurs first) as outlined in Section 7.6
- Barriers to LDTCI
- Interventions and outcomes

Five Months After Registration (+/- 15 days)

Second Medical Record Review
- Record results of preoperative pulmonary function tests (PFTs)
- Confirm receipt of LDTCI
- Confirm receipt of Surgical and/or Radiation Oncology Consultation
- Confirm time to LDTCI (in patients who received LDTCI)
- Confirm time to death

Thirteen Months After Registration (+/- 15 days)

Third/Final Medical Record Review
- Record results of preoperative PFTs (unless recorded at Second Medical Record Review)
- Confirm receipt of LDTCI
- Confirm receipt of Surgical and/or Radiation Oncology Consultation
- Confirm time to LDTCI (in patients who received LDTCI)
- Confirm time to death
- Record clinical tumor stage (American Joint Committee on Cancer Tumor-Node-Metastasis [AJCC TNM] stage) at presentation
- Record histologic tumor classification (if proven tumor, preoperatively [i.e., biopsy] and/or postoperatively [i.e., S/P resection]
7.4.3 **MUSC HCC staff use only**

**Baseline**

- Administer baseline survey

**Three Months After Registration**

- Administer Periodic Assessment of Cancer Treatment and Disease Status
- Administer follow-up questionnaire

**Six Months After Registration**

- Administer follow-up survey
- Administer Periodic Assessment of Cancer Treatment and Disease Status

**Nine Months After Registration**

- Administer Periodic Assessment of Cancer Treatment and Disease Status

**Twelve Months After Registration:**

- Administer follow-up survey
- Administer Periodic Assessment of Cancer Treatment and Disease Status
7.5. Study Calendar/Study Parameters Table

Table A: Site Use Only:

<table>
<thead>
<tr>
<th>Evaluation/Procedure</th>
<th>Pre-Baseline</th>
<th>Baseline</th>
<th>3 months</th>
<th>4 months</th>
<th>5 months</th>
<th>13 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Screener</td>
<td>X</td>
<td></td>
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<tr>
<td>Eligibility Screener</td>
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<tr>
<td>Informed Consent</td>
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<td></td>
</tr>
<tr>
<td>Wake Forest Registration</td>
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<td></td>
</tr>
<tr>
<td>Medical Record Review:</td>
<td>X</td>
<td>X**</td>
<td>X**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Confirm eligibility</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Confirm comorbidities</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PN Log (Navigator Sites Only)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Barriers to LDTCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Interventions and outcomes</td>
<td>Weekly until deemed not eligible*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*At least weekly until deemed not eligible for LDTCI by physician(s), receipt of LDTCI, 4 months (16 weeks, 112 days) after NSCLC diagnosis, or death (whichever occurs first)

** 5 and 13 months Medical Record Review should be obtained +/- 15 days.

Table B: MUSC Staff Use Only:

<table>
<thead>
<tr>
<th>Evaluation/Procedure</th>
<th>Baseline</th>
<th>3 mos</th>
<th>6 mos</th>
<th>9 mos</th>
<th>12 mos</th>
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</thead>
<tbody>
<tr>
<td>Baseline and Follow-up Survey:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- Quality of life (14 items)</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
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<tr>
<td>- Anxiety (7 items)</td>
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<td>√</td>
<td>√</td>
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<td></td>
</tr>
<tr>
<td>- Self-efficacy in communication with health care providers (12 items)</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>- Trust in physician (11 items)</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>- Risk attitude (3 items)</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Belief that exposure to air during surgery causes lung cancer to spread (1 item)</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>- Intention to receive LDTCI (1 item)</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Satisfaction with decision (6 items)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Social support (12 items)</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
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</tr>
<tr>
<td>- Fatalism (5 items)</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>- Faith (5 items)</td>
<td>√</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>- Barriers to care (20 items)</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>- Comorbidity index (10+ items)</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>- Tobacco use (2 items)</td>
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<td>√</td>
<td>√</td>
<td>√</td>
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<tr>
<td>- Sociodemographics (10 items)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>- Satisfaction with care received</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>√</td>
</tr>
</tbody>
</table>
(28 items)

<table>
<thead>
<tr>
<th>- Intervention arm only:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Satisfaction with patient navigation services (9 items)</td>
<td>√</td>
</tr>
</tbody>
</table>

**Periodic Assessment**

| - Consultation with physician(s)/treatment(s) | √ | √ | √ | √ |
| - Vital/disease status                       | √ | √ | √ | √ |

---

### 7.6. Off Intervention Criteria

Participants in the intervention arm may go “off intervention” for the following reasons:

- Deemed *not* eligible for LDTCI by their physician(s) *after* registration
- Receipt of LDTCI
- 4 months (16 weeks, 112 days) have elapsed from the date of NSCLC diagnosis

### 7.7. Off Study Criteria

Participants may go ‘off-study’ for the following reasons:

- Deemed *not* eligible for the study *after* registration (See section 4.2 Study Participant Eligibility Criteria)

**Prior to LDTCI:** If patient does *not* have early stage NSCLC *after registration but prior* to LDTCI they may go off-study. (e.g., via lung biopsy).

**After LDTCI** - When surgical resection is performed, if patient does *not* have early stage NSCLC they *will remain* in the study. (e.g., benign lesion, stage III-IV NSCLC, SCLC, etc)

- The protocol intervention and any protocol required follow-up period is completed
- Adverse event/serious adverse event
- Medical contraindication
- Withdrawal of consent
- Lost to follow-up
- Death

### 7.8. Quality Assurance

#### 7.8.1. Evaluating the Treatment Fidelity of the EPDPN Intervention.

Telephone logs will be maintained to measure the number, length, and type of contact (telephone or in person) with each participant. Each PN will maintain a tracking log to record the amount of time spent with each participant and the barriers that were addressed. The PNs will also use the log to record the amount of time spent in contact with clinical staff/agencies/community resource personnel to identify resources to address the barriers faced by participants. We will use these data to identify which specific types of barriers were overcome via the navigation intervention. We will also use the data to measure dose and type of delivery (i.e., the amount of navigation services that each participant requested and received). In addition, all navigated participants will be queried on the appropriateness and quality of the intervention.
8. PROTOCOL SPECIFIC TRAINING REQUIREMENTS

8.1. Patient Navigator Intervention Training Description

We will train PNs from each intervention site to conduct the intervention. Training will be conducted in person and/or web-based modules and/or webinars. Each PN will undergo more intensive training in Year 1, as well as yearly "refresher" training in Years 2-5, as needed. PNs will also participate in regularly scheduled teleconferences with the PIs and MUSC HCC study staff, as noted above.76

The training will be modeled after Dr. Beth Calhoun’s NCI-funded PN training module that is based on Adult Learning Theory (Knowles), Social Cognitive Theory (Bandura), social support theory, and competency evaluation. The training will consist of a comprehensive, interactive program covering the PN’s role, communication with patients (with active listening), cancer care education, access to community resources, ethics and privacy practices, professional boundaries, and the patient navigation process.

The training will include a segment on providing culturally competent care. The training will begin with Cancer 101, consisting of an overview of lung cancer, including its definition and nomenclature, etiology, cancer disparities, myths and misconceptions, and cancer control. The PN’s role as a provider of various types of social support (informational, emotional, and instrumental) will be described. Existing community resources to address barriers to care will be presented. We will use an interactive teaching module in which the PNs will be asked to list obstacles to care that they or their family members/friends have encountered and discuss ways to overcome these obstacles. Vignettes of typical patient situations will be examined to determine how a PN might assist patients in overcoming these situations.76

To accommodate different learning styles, the training may include different modes of information dissemination, including didactic lecture, role play, small group discussion, and observed structural video examination. The training will emphasize the importance of adequate recordkeeping using standardized tracking forms and databases across study sites. The PNs will be trained to document all patient encounters using the SOAP (Subjective, Objective, Assessment, and Plan) method used by many health care providers. After the initial training, the PNs will participate in periodic, scheduled navigator teleconferences. During each teleconference, PNs will share their experiences and collectively develop solutions to address issues.77

9. SPECIMEN MANAGEMENT: N/A

10. REPORTABLE ADVERSE EVENTS/SERIOUS ADVERSE EVENTS

Only report unexpected adverse events that are related to the Enhance, protocol driven, patient navigation (EPDPN) intervention.

Only report unexpected hospitalizations, grade 4 and 5 that are related or not related to the Enhance, protocol driven, patient navigation (EPDPN) intervention.
• **Serious Adverse Events (SAE) reporting begins at signing of consent.** Serious Adverse Events occurring within 30 days of study completion must be reported via FDA Form 3500 (MedWatch).

Fax MedWatches to WF NCORP RB DM (fax: (336) 713-6476) for data entry into ORIS and fax to MUSC HCC (fax: (843) 876-2573).

### 11. STUDY MONITORING

#### 11.1. Data Management

Study data will be entered into MUSC’s web-based REDCap data management system, where they can be accessed by the MUSC HCC and WF NCORP RB data analysts and statisticians for cleaning and analysis. WF NCORP RB staff and statisticians will have access to REDCap as needed for data audit and analysis purposes.

REDCap is a secure, web-based application designed exclusively to support data capture for research studies. REDCap provides: 1) an intuitive interface for data entry (with data validation); 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R); 4) procedures for importing data from external sources; and 5) advanced features, such as branching logic and calculated fields. The REDCap project ([http://project-redcap.org/](http://project-redcap.org/)) was initiated at Vanderbilt University and includes more than 70 active institutional partners from Clinical and Translational Science Award (CTSA), GCRC, RCMI funded institutions, including MUSC, and others through a collaborative international consortium.78

MUSC’s REDCap system is run through the university’s CTSA. The REDCap data management system will be available for use by the SSCs and PNs at all of the study sites. The REDCap program will allow the SSCs and PNs at each study site, as well as MUSC HCC study staff, to input data, including necessary protected health information, over a secure web connection with authentication and data logging. MUSC HCC study staff will conduct the telephone-administered surveys, record the survey data on hard copy forms, and subsequently enter the data into the web-based REDCap system.

Study information will be exchanged via secure telephone, e-mail, and fax lines. For additional information that may need to be uploaded (e.g. chart reviews that are not faxed), the MUSC approved Filelocker system may be used. Filelocker is a web based secure file sharing application that facilitates easy file sharing between users at an organization and promotes secure data sharing habits. Filelocker uses HIPAA and FERPA compliant data sharing including the ability to send encrypted messages securely.

#### 11.2. Data Management Schedule

The Wake Forest NCORP **Eligibility checklist/Registration Form should be completed on-line for the patient to be registered and receive NCI credit.** Data forms will be submitted according to the timetable below: via fax to:

WF NCORP RB (336) 713-6476   AND   MUSC HCC Fax to (843) 876-2573
### Form Submission Schedule

<table>
<thead>
<tr>
<th>Form</th>
<th>Submission Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signed Consent Form</td>
<td>At baseline, to MUSC HCC and WF NCORP RB</td>
</tr>
<tr>
<td>MedWatch Forms</td>
<td>At time of occurrence, to MUSC HCC and WF NCORP RB</td>
</tr>
</tbody>
</table>

### 11.3. Case Report Forms

Participant data will be collected using protocol-specific case report forms (CRF).

### 11.4. Source Documents

Source documents are the original signed and dated records of participant information (e.g., the medical record, shadow chart) which may include electronic documents containing all the information related to a participant’s protocol participation. Source documents are used to verify the integrity of the study data, to verify participant eligibility, and to verify that mandatory protocol procedures were followed. An investigator and other designated staff are required to prepare and maintain adequate and accurate documentation that records all observations and other data pertinent to the investigation for each individual participating in the study. All data recorded in the research record (including data recorded on CRFs) must originate in the participant’s medical record, study record, or other official document sources.

Source documents substantiate CRF information. All participant case records (e.g., flow sheets, clinical records, physician notes, correspondence) must adhere to the following standards:

- Clearly labeled in accordance with HIPAA practices so that they can be associated with a particular participant or PID;
- Legibly written in ink;
- Signed and dated in a real time basis by health care practitioner evaluating or treating the participant; and
- Correction liquid or tape must not be used in source documents or on CRFs.
- Corrections are made by drawing a single line through the error. Do not obliterate the original entry. Insert the correct information, initial, and date the entry.

All laboratory reports, pathology reports, x-rays, imaging study and scans must have:

- Complete identifying information (name and address of the organization performing, analyzing, and/or reporting the results of the test); and
- Range of normal values for each result listed.

### 11.5. Data and Safety Monitoring Board (at WF NCORP RB sites)

The WF NCORP RB Data Safety Monitoring Board meets every six months to review protocols. The Board includes members demonstrating experience and expertise in oncology, biological sciences and ethics. The DSMB report is generated by the WF NCORP RB statistician. Protocol specific areas of review may include the following: Study
Objectives; Patient Accrual; Patient Status and Retention; Study Status; Last Contact Status; Patient Compliance; Number of Biopsies/Labs as needed; Patient Characteristics; Summary of Observed Toxicities; Adverse Events; Date, Event briefly described, Relationship to intervention, Arm assigned; Summary of Primary and Secondary Measures.

11.6. Record Retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.), as well as IRB records and other regulatory documentation will be retained by the investigators in a secure storage facility in compliance with HIPAA.

Record retention should be 5 years after the study is discontinued for studies without an IND (21 CFR 312.62).

11.7. CDUS Reporting

The WF NCORP RB Data Management Center will submit quarterly reports to DCP/CTEP by electronic means using the Clinical Data Update System (CDUS)

12. STATISTICAL CONSIDERATIONS

12.1. Study Design/Endpoints

This is a two-arm, stratified cluster-randomized, cancer care delivery trial to determine if an EPDPN intervention will improve rates of LDTCI in AAs with recently diagnosed, probable/proven, early stage NSCLC in the southern US versus usual care.

All primary and secondary endpoints are defined in Section 3.3 (Patient Outcome Measures).

12.2. Sample Size/Accrual Rate

Subjects will be assigned to either the EPDPN intervention (100 subjects) or usual care (100 subjects) based on randomization at the site level. We assume a null LDTCI rate of 60%. This null rate is based on 2000 – 2011 data from the American College of Surgeons National Cancer Data Base (http://www.facs.org/cancer/ncdb/), in which the average resection rate among African Americans with stage I-II NSCLC in the southern US (i.e., “South” region, based on US Census Bureau definitions) was 60%. We are targeting a 20% improvement in receipt of LDTCI (that is, an alternative rate of 80%), an effect size we consider reasonable based on the range of observed state-level, resection rates among white patients with stage I-II NSCLC in the southern US in the NCDB during the same time period, as well as published randomized trials which have demonstrated the efficacy of navigation interventions to improve rates of treatment in minority cancer patients.25,31

Because this is a cluster-randomized trial, our power analysis accounts for the lack of independence among measures obtained from patients enrolled from the same site. In a review of cluster randomized trials, Eldridge and colleagues76 report a median intra-cluster
correlation (ICC) of 0.04. We therefore conservatively assume an ICC of 0.05, and an average of 10 patients enrolled from a given site. This design yields 83% power to detect an improvement in the rate of LDTCI from 60% to 80% based on a pooled z-test of two proportions with one-sided $\alpha = 0.05$. Sample size calculation and power analysis were performed using PASS 2008, version 08.0.13.80

Accrual is expected to be approximately 10 patients per month. Targeted accrual should be met in approximately 20 months. A maximum of 200 patients will be enrolled on this trial. Patients will be followed/contacted for 12 months. After the 13th month, final, medical record review (and until the end of the study period), time to death will be assessed via cancer registries at each study site (and/or the Social Security Death Index will be queried in patients lost to follow-up).

**12.3. Stratification and Randomization**

We will minimize the possibility of contamination by randomizing by study site rather than by participant. This will reduce the likelihood of cross-contamination between patients assigned to the usual care group versus the EPDPN intervention group.

Study sites will be stratified by the average number of AAs with stage I-II NSCLC seen per year (based on historical cancer registry data from that site) with a threshold of <10 versus $\geq$10, based on reported associations between hospital surgical volumes, hospital structures/processes, and surgical outcomes.81,82 Sites will be randomized to either the EPDPN intervention or usual care, and all patients recruited by a particular study site will receive that study site’s assigned care.

Sites will be randomized to either EPDPN or usual care based on a stratified permuted block randomization scheme, with randomly selected block sizes of 2 or 4. Only the study statistician will have access to the randomization list.

**12.4. Analysis of Primary Endpoint**

**12.4.1. Receipt of LDTCI**

To evaluate the impact of the EPDPN intervention on rates of LDTCI, we will compare rates of LDTCI between the two arms using a Rao-Scott chi-square test, equivalent to a design-adjusted chi-square test.83 Here we adjust for both the clustering of patients within site, and the stratification of sites by size. (Rao and Scott demonstrate the utility of their test for Mantel-Haenszel-type comparisons of proportions obtained from clustered binary data.) Additionally, we will construct point and interval estimates of LDTCI rates for each study arm, with standard errors (and by extension, confidence limits) appropriately adjusted for the correlation among measures obtained from the same site.84

**12.4.2. Modifying Effects of Income and Urban-Rural Residence on Receipt of LDTCI**

We will evaluate the modifying effects of income and urban-rural residence on the relationship between the intervention and rates of LDTCI using generalized estimating equations with a logit link function and an exchangeable correlation
structure. Specifically, we will model the log odds of receipt of LDTCI as a function of study arm, household income (low versus moderate or high), study arm-by-income interaction, and a factor for stratification by size. Effect modification will be considered meaningfully present if the corresponding interaction p-value is statistically significant at level 0.05, and LDTCI rates and corresponding odds ratios subsequently will be summarized separately for low income and moderate-high income subjects. We will use a similar approach to examine effect modification by urban-rural residence.

12.5. Analysis of Secondary Endpoints

12.5.1. Receipt of Surgical and/or Radiation Oncology Consultation

Surgical and/or radiation oncology consultation rates will be analyzed as described in Section 12.6.1 for the primary endpoint.

12.5.2. Time to LDTCI

Time to LDTCI will be analyzed only for the subset of patients (in either arm) receiving LDTCI. To assess the impact of the intervention on time to LDTCI, we will use a gamma-frailty hazard regression model with site-specific frailties \(^85\) to model the hazard of LDTCI as a function of trial arm and a factor for stratification by size. Here, the frailty is a multiplicative term modifying the hazard such that a frailty greater (less) than 1 indicates sites with greater (less) than average hazard. That is to say, subjects from a given site are more (or less) likely to receive LDTCI than average. The impact of navigation will be evaluated based on the direction, magnitude, and statistical significance of the trial arm coefficient. This estimated coefficient and standard error will be used to construct a hazard ratio with corresponding 95% confidence interval. Kaplan-Meier curves by trial arm will be constructed to provide graphical displays of time to LDTCI, and to construct estimates of median time to LDTCI by trial arm.

12.5.3. Satisfaction with Care Received

Satisfaction with care received is a continuous measure evaluated at 6 months post-enrollment. This endpoint will be analyzed using generalized estimating equations with an identity link function and an exchangeable correlation structure. Specifically, we will model satisfaction with care received as a function of study arm and a factor for stratification by size. The impact of navigation on satisfaction with care received will be evaluated based on the direction, magnitude, and statistical significance of the trial arm coefficient.

12.5.4. Time to Death

Overall survival (OS) will be analyzed as described in Section 12.6.4 for the secondary endpoint of time to LDTCI. However, OS will be analyzed using the ITT analysis set (see Section 12.7.1). Subjects still alive at the last date of follow-up will have their survival times censored. Kaplan-Meier curves by trial arm will be constructed to provide graphical displays of survival times, and to construct estimates of median OS by trial arm.
12.6. Analysis of Tertiary Endpoints

12.6.1. Analysis of Barriers to LDTCI

Barriers to LDTCI will be analyzed both on the original Likert scale, and as dichotomized variables. Comparisons on the original scale between trial arms at specific time points will be performed using Wilcoxon rank-sum tests. Analysis of the dichotomized barriers measures will be performed using generalized linear mixed effects models with logit link function, and trial arm, time (baseline, 3, 6 or 12 months), trial arm-by-time interaction, and size stratification as fixed effects. Models will also include both site- and subject-specific random effects to adjust for the lack of independence induced by the trial’s design (clustering of subjects within sites) and longitudinal evaluation of secondary endpoints (clustering of measures within subjects), respectively. Comparisons between trial arms and between specific time points will be performed using model-based linear contrasts.

12.6.2. Analysis of Mediators

Mediating factors will be analyzed using linear mixed effects models with trial arm, time (baseline, 3, 6 or 12 months), trial arm-by-time interaction, and size stratification as fixed effects. Models will also include both site- and subject-specific random effects to adjust for the lack of independence induced by the trial’s design (clustering of subjects within sites) and longitudinal evaluation of secondary endpoints (clustering of measures within subjects), respectively. Comparisons between trial arms and between specific time points will be performed using model-based linear contrasts.

12.7. Reporting and Exclusions/Analysis Sets

12.7.1. Intent to treat set

The intent to treat (ITT) set comprises all eligible patients enrolled to either the EPDPN intervention or usual care. For the ITT analysis of the primary endpoint, eligible patients enrolled in the study for whom receipt of LDTCI is unknown due to patient drop out or loss to follow up will be treated as failures. Similarly, if receipt of surgical and/or radiation oncology consultation is unknown for enrolled subjects due to drop out or loss to follow up, this secondary endpoint will be treated as a failure for the ITT analysis. For patients in either arm still alive at the time of last follow-up, survival times will be censored.

Every effort will be made to minimize the number of drop-outs, beginning with the accrued participants. If a patient seems unwilling to participate, they will not be pressed to participate. In addition, participants who miss one follow-up survey will continue to be contacted at the planned timepoints for the subsequent, follow-up surveys.

12.7.2. Time to LDTCI set
Time to LDTCI is defined only for the subset of patients (in either study arm) receiving LDTCI.

12.8. Evaluation of Toxicity: N/A

12.9. Evaluation of Response

All participants included in this study will have their outcomes assessed at baseline and at 3, 6, 9 (some outcomes), and 12 months. Efforts will be made to collect these data even if participants refused on a previous occasion. Data should only be missing for those who withdraw consent or expire. As noted earlier, all eligible randomized participants will be included in the analyses of treatment efficacy.

12.10. Interim Analyses

There will be no formal interim analyses for efficacy or futility for this study. However, the HCC DSMB (for the non-WF NCORP RB sites) and the WF DSMB (for the WF NCORP RB sites) will independently review study progress twice yearly for accrual, retention, adherence, data quality, and safety. Descriptive reports for the DSMBs will consist of summary statistics (means, standard deviations, proportions, etc.) for participant characteristics and outcome measures, actual versus projected accrual, participation by various sites, and quality control information (retention, adherence, missing data, etc.). Tables, graphs, and charts will be used to illustrate the data when appropriate.

13. PROTECTION OF HUMAN SUBJECTS


All participants will be assigned a unique identifier number, which will be used on all study materials. Only one key linking patient names to study materials will be maintained in a locked cabinet in the locked offices of the MUSC HCC PI. Access to the computerized datasets generated as a part of this study will be restricted, through the use of passwords, to study personnel identified by the principal investigator as requiring access. In addition, data files containing names, addresses, and telephone numbers of study participants will have separate passwords and will be accessible only by those personnel who will need this information in order to contact participants. Study results will be reported in aggregate format only.


The potential risk to participants is low. We anticipate that the only risk to participants will be mild psychological discomfort with the interview or survey process. We will take several steps to minimize this risk: (1) all participants will be given the option to terminate participation at any point in the study. We will build prompts into the beginning of each interview that will ask participants whether they are comfortable continuing with the study. In addition, if, at any point during the course of the study, a participant becomes agitated, emotionally distressed, or otherwise indicates the need for clinical mental health intervention, he or she will be referred to appropriate clinical mental health resources at his or her study site.
13.3. Potential Benefits of the Proposed Research to the Participants and Others.

Participants will receive an honorarium in the form of a $50 gift card at each survey data collection point (baseline, 3 months, 6 months, and 12 months). These stipends are designed to compensate participants for their time spent in the study. The investigators cannot guarantee any direct health benefits to participants from participation other than the benefits provided by usual care.

13.4. Importance of the Knowledge to be Gained.

The proposed work is significant for many reasons. First, lung cancer is the leading cause of cancer deaths in the US. Second, the population of the southern US is racially diverse, with AAs comprising a significant portion of the population. Third, AAs are disproportionately affected by lung cancer. Developing an intervention to improve rates of LDTCI is highly innovative. The intervention we develop could play a major role in reducing these health disparities. Fourth, the southern US has large urban as well as rural geographic areas. Therefore, in this study, we will have the opportunity to assess the effect of urban versus rural residence on the study outcomes.

13.5. Data and Safety Monitoring Plans

13.5.1. Data and Safety Monitoring Plan at MUSC HCC

The MUSC HCC has a Protocol Review and Monitoring System that includes a Data and Safety Monitoring Committee (DSMC). The DSMC is charged with the ongoing review of all cancer research studies involving diagnosis, treatment, prevention and control. This committee meets regularly to review the priorities and progress of each study and recommends action to be taken as needed.

The DSMC is responsible for monitoring data quality and patient safety for all interventional investigator-initiated trials (IITs) at the HCC. A summary of DSMC activities follows:

- Reviews all Protocol Review Committee (PRC)-approved interventional IITs conducted at HCC for safety, data and compliance monitoring at intervals defined in the HCC Data Safety Monitoring Plan
- Reviews all serious adverse events
- Has the authority to recommend closure and/or suspension for trials on which there are safety or trial conduct issues and may submit recommendations for corrective actions to the HCC Clinical Research Oversight Committee (CROC).

The PRC will review this study annually for progress and performance. If the study has not achieved at least 50% of the targeted enrollment goal during each review period, the PIs will be asked to provide an explanation and study recruitment plan.

The DSMC recommendations for modifications to the trial (if requested) are forwarded to the principal investigator as well as HCC’s Clinical Research Oversight Committee (CROC). The PIs would be notified of this recommendation in order that they may alert all investigators involved in the trial with regard to the potential action. At that time the PIs would submit to the DSMC additional information that could affect the Committee's decision. In the event the investigators wished to appeal the DSMC
recommendation, it will be reviewed by the CROC. The CROC would notify the PIs of their decision. The DSMC would notify the MUSC IRB and the PIs are responsible for notifying all Investigators involved with the study, the Supporter and/or funding agency and provide written documentation of these notifications to the CROC.

The DSMC will oversee trial processes including monitoring of recruitment, follow-up, trial close-out, and will assure that the participants in the trial are treated ethically (e.g., no undue persuasion to participate, no breaches of confidentiality, etc). As such, the DSMC will play an essential role in protecting the safety of study participants, and in assuring the integrity of study data. The DSMC will submit its recommendation to the MUSC HCC Protocol Review Committee for review and approval.

The DSMC will include experienced investigators who are external to the proposed study. They will report to the PIs, the local IRB, and the National Institutes of Health (NIH) if patient harm is observed. If deemed necessary, they will work with the PIs to alter the protocol, as appropriate.

Adverse events are defined as "unanticipated problems" involving risks to participants. An adverse event form will be developed by the investigators and will be completed by study staff if needed. Each adverse event will be reported immediately to the appropriate local IRB. The reporting of adverse events is in addition to, and does not supplant, periodic reports to the IRB at intervals appropriate to the degree of risk in the study, generally, an annual report. In addition, the PIs will prepare a written summary report whenever a DSMC review has taken place. The DSMC will meet once during each year of the proposed 5-year study.

Additionally, the PIs will oversee study processes and will ensure that informed consent is scrupulously obtained and that the protocol is maintained at the MUSC IRB as well as the IRBs at each study site. They will review data quality every month to assure that the study continues to be feasible and of high quality. The PIs will also review data on participant enrollment, study procedures, forms completion, data quality, and other measures of adherence to the study protocol.

13.5.2. Data and Safety Monitoring Plan at WF NCORP RB sites

See Section 11.5.

13.6. Quality Assurance and Data Management

13.6.1 Quality Assurance

Several mechanisms have been established to ensure high-quality study data. First, prior to administering the surveys, MUSC HCC study staff will receive training on interviewing. MUSC HCC study staff will be trained to administer the surveys in a standardized manner. The in-depth training sessions will include role-playing of standardized questions and probes, full practice interview sessions with the research team, and pilot interviews with research participants. The Program Coordinator will assist the MUSC HCC study staff with the survey interviews on an as-needed basis. A question-by-question interviewing manual has been developed. Standardization of interviewing procedures will be re-emphasized every three months. Second, initial
interviews and procedures conducted by MUSC HCC study staff and will be closely supervised by the PIs. Third, completed surveys will be reviewed for completeness, legibility, and logical consistency. Fourth, the MUSC HCC study staff will review the data collection forms for completeness before data are entered, and will re-contact participants to obtain any missing data. Fifth, the MUSC HCC study staff will be trained to enter the data from the surveys in a standardized format. Once the data have been cleaned, they will be analyzed. Sixth, PNs at each intervention site will undergo more intensive training in Year 1, as well as yearly "refresher" training in Years 2-5, as needed. PNs will also participate in regularly scheduled teleconferences with the PIs and MUSC HCC study staff, as noted in Section 8.1.

13.6.2. Data Management.

See Section 11.1.

13.6.3 Evaluating the Treatment Fidelity of the Patient Navigation Intervention.

See Section 7.8.1.

13.7. Human Subjects Training

Participation of human subjects in research is under the jurisdiction of federal regulations (45 CFR 46 and 21 CFR 50 and 56). MUSC investigators are granted the privilege of working with human subjects under normal assurance to the government that such research complies with regulations protecting human subjects. The university has a federal-wide assurance for research with human subjects (FWA 00001888, 02/06/2002-10/06/2008), and is in compliance with federal policy governing use of human subjects. Individuals involved in human subject research at MUSC are required to complete the Collaborative IRB Training Initiative (CITI) offered on-line by the University of Miami. All human subject protocols are reviewed through an academic IRB process. The MUSC Office of Research Integrity coordinates the activities of three IRB committees, involving faculty members as well as representatives of the business, legal, ethical, religious, and civic communities.


The Study includes a randomized trial, is registered in ClinicalTrials.gov, and recommended guidelines will be followed. The Authorized Organizational Representative of MUSC assures compliance with Public Law 110-85, enacted 09/27/2007. The law amends the Public Health Service Act to expand the scope of clinical trials that must be registered in ClinicalTrials.gov. It also increases the number of registration fields that must be submitted, requires certain results information to be included, and sets penalties for noncompliance.
REFERENCES


