A Preliminary Study of Prophylactic Fentanyl Buccal Tablet (FBT) for Exercise-Induced Breakthrough Dyspnea

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A. Study Objectives

Primary objective:
To determine the **variances of the change in intensity** of exercise-induced breakthrough dyspnea (numeric rating scale) of prophylactic fentanyl buccal tablet (FBT) and placebo between the first and second 6 minute walk tests. The variance will allow us to properly power a future definitive study.

Secondary objective:

1. To **compare the final dyspnea scores** at the end of the two walk tests, after adjusting for distance walked. A similar comparison will be performed for placebo. We *hypothesize* that FBT is superior to no FBT in reducing dyspnea at the end of a 6 minute walk test.

2. To **compare the intensity** of exercise-induced breakthrough dyspnea, walk distance, neurocognitive function, and physiologic parameters (respiratory rate, O2 saturation) of patients administered prophylactic FBT given 30 minutes before a 6 minute walk test to that of patients given placebo 30 minutes before a 6 minute walk test. We *hypothesize* that FBT is superior to placebo in reducing dyspnea and improving walk distance and physiologic parameters.

B. Background

B.1. Significance of Dyspnea. Dyspnea is a subjective awareness of difficulty breathing, which may be associated with the distressing sensation of suffocation. It is one of the most common and most feared symptoms among cancer patients, occurring in up to 70% of patients in the last 6 weeks of life (Ben-Aharon et al. 2008). Dyspnea is associated with fatigue, anxiety, decreased function and quality of life, and increased mortality (Hauser et al. 2006, Maltoni et al. 2005).

In a study examining 70 patients with dyspnea, 43 (61%) reported breakthrough (episodic or incidental) dyspnea only, 13 (19%) had constant dyspnea only, and 14 (20%) experienced both constant and breakthrough dyspnea. A substantial proportion of the patients with breakthrough dyspnea (18/57, 32%) presented with 5 or more episodes per day, and the majority of episodes lasted <10 minutes (Reddy *et al.* 2009). Breakthrough dyspnea is particularly challenging to treat because of its transient and episodic nature.

Exercise-induced dyspnea (or shortness of breath on exertion) is a subtype of breakthrough dyspnea. Breakthrough dyspnea has 4 major triggers: exertion, emotional changes, the environment (e.g. altitude, smog), and spontaneous/idiopathic. Because many cancer patients experience severe shortness of breath with activities (i.e. walking), they have to limit their function significantly. In a recent study conducted by our group, we found that a vast majority of patients (81%) had breakthrough dyspnea. Specifically, dyspnea affects patients' general activity, walking ability, normal work, sleep, mood, relations with others, and enjoyment of life (Reddy *et al.* 2009).

B.2. The Current Management of Dyspnea. The current management of dyspnea involves treatment of any reversible causes and supportive measures to minimize the sensation of dyspnea, including treatments such as oxygen, opioids, bronchodilators, and corticosteroids (Ben-Aharon *et al.* 2008, Cranston *et al.* 2008, Jennings *et al.* 2002). A majority of the studies on cancer-related dyspnea so far have focused on patients with dyspnea at rest. In a crossover randomized controlled trial, Bruera et al. compared subcutaneous (SC) morphine and placebo in 10 patients with advanced cancer who had dyspnea at rest. Subcutaneous morphine was found to be superior to placebo for relief of dyspnea (Bruera *et al.* 1993). This finding was replicated by Mazzocato et al. in another randomized controlled trial with similar design (Mazzocato *et al.* 1999). A Cochrane meta-analysis also showed a statistically significant positive effect of opioids on the sensation of breathlessness (p=0.0008), supporting the use of oral or parenteral opioids for treatment of dyspnea in patients with advanced disease (Jennings *et al.* 2002).

Although systemic opioids are established for management of dyspnea at rest, there are currently no evidence-based options for breakthrough dyspnea. In a case series, Bruera et al. reported the use of rescue morphine given subcutaneously for 312 episodes of breakthrough dyspnea in 45 cancer patients. After 30 minutes, 90% reported no to mild dyspnea (Bruera *et al.* 1993). Based on this study, most clinicians use a dose similar to the rescue opioid dose for breakthrough pain (i.e. 10-20% of total daily dose) to manage breakthrough dyspnea. However, a more recent double-blind randomized controlled trial comparing systemic fentanyl (oral or subcutaneous), nebulized fentanyl, and nebulized saline for breakthrough dyspnea found no significant difference in dyspnea relief at 10 minutes between the treatment arms (Charles *et al.* 2008). One of the reasons may be due to the short duration for the primary endpoint (10 minutes). To date, the evidence for opioid use for breakthrough dyspnea remains limited (Table 1). Further research is necessary to improve the management of this distressing and debilitating symptom.

Table 1. Studies of Opioids for Breakthrough Dyspnea

Study	Methodology and patients	Agent and dose	Outcome
Bruera et al. Ann Intern Med 1993 (Bruera *et al.* 1993)	Prospective case series (45 cancer patients [pts])	SC morphine 312 doses given (same dose as pain breakthrough)	After 30 minutes, 90% reported no-mild dyspnea; 5% mod-severe dyspnea
Benitez-Rosario et al. JPSM 2005 (Benitez-Rosario *et al.* 2005)	Retrospective case series (4 cancer pts)	OTFC 800mg/1200mcg 60mg/800mcg 120mg/600mcg 15mg/400mcg	RR decreased Dyspnea decreased by 90-100% in 20-60 minutes
Sitte et al. JPSM 2008 (Sitte and Bausewein 2008)	Retrospective case series (1 cancer pt, 2 heart failure pts)	Intranasal fentanyl 1/6 of MEDD	RR decreased, improved O_2 saturation in all 3 patients Dyspnea scores not reported
Gauna et al.	Prospective case	OTFC	RR decreased

JPM 2008 (Gauna *et al.* 2008)	series (2 COPD pts, 2 cancer pts) 10 episodes	30mg/200mcg 720mg/400mcg 20mg/200mcg 24mg/200mcg	Dyspnea decreased by 90-100% in 20-60 minutes
Charles et al. JPSM 2008 (Charles *et al.* 2008)	Prospective, double blind crossover RCT (20 cancer pts)	Systemic hydromorphone Nebulized hydromorphone Nebulized saline	Dyspnea decreased similarly in all 3 arms (1.0, 0.9, 0.8)

Abbreviations: RR=respiratory rate, OTFC=oral transmucosal fentanyl citrate, SC=subcutaneous

B.3. Rapid Onset Opioids for Breakthrough Dyspnea. The episodic and transient nature of breakthrough dyspnea makes fast onset opioids an attractive option. Administration of opioids intravenously or subcutaneously can allow rapid delivery of the drug, although many patients do not have access to these routes at home. Fentanyl is a highly lipophilic compound. Over the past decade, there has been active development of fentanyl, including delivery by the transmucosal (oral transmucosal fentanyl citrate [OTFC], Actiq), buccal (Fentora), and intranasal (Lazanda, Instanyl) formulations (Gordon and Schroeder 2008, Lecybyl and Hanna 2007). These fentanyl formulations have been successfully used to manage breakthrough pain (Christie *et al.* 1998, Coluzzi *et al.* 2001, Fallon *et al.* 2011, Farrar *et al.* 1998, Mercadante *et al.* 2007, Portenoy *et al.* 1999, Portenoy *et al.* 2006, Portenoy *et al.* 2010, Slatkin *et al.* 2007), although their role in breakthrough dyspnea has only been reported in a handful of studies. Two small retrospective case series reporting on the use of transmucosal and intranasal fentanyl (Benitez-Rosario *et al.* 2005, Sitte and Bausewein 2008) and one prospective series examining the use of OTFC (Gauna *et al.* 2008) suggest significant improvement in breakthrough dyspnea with these agents. Randomized controlled trials are urgently needed to confirm these findings with rapid onset opioids.

FBT is a particularly attractive option for breakthrough dyspnea. It was approved by the US Food and Drugs Administration in 2006 for “breakthrough pain in opioid-tolerant patients with cancer”, and represents an alternative delivery system for fentanyl that also utilizes a transmucosal route like OTFC. Pharmacokinetic studies directly comparing FBT and OTFC have demonstrated that fentanyl enters the systemic circulation faster and to a greater extent with the effervescent system. It has an absolute bioavailability of 65% (Lecybyl and Hanna 2007). The time to maximal effect (T_{max}) was between 0.58-0.75 hour (Darwish *et al.* 2006, Lecybyl and Hanna 2007). FBT has been found in clinical trials to provide greater and more rapid pain relief, and reduces pain better than placebo (Portenoy *et al.* 2006, Slatkin *et al.* 2007). In a prospective series, Weinstein et al. reported on the long term safety of 197 patients who received FBT during maintenance phase (median of 122 days). Nausea (32%), vomiting (24%), fatigue (18%), constipation (15%), and headaches (15%) were the most common side effects (Weinstein *et al.* 2009).

C. Experimental Approach

C.1. Overall Study design. This is an investigator-initiated study supported by Teva Pharmaceutical Industries**.** We propose a 2-arm, double blind, parallel randomized controlled trial of FBT and placebo for cancer patients with breakthrough dyspnea (Figure 1). The main goal of this study is to determine the effect size for both FBT and placebo arm to inform a larger, adequately powered confirmatory randomized controlled trial. After study consent, eligible patients will be asked to complete a number of surveys and a 6-minute walk test at baseline, rest until they return to baseline dyspnea, and then do another 6-minute walk test after they have been given either FBT or placebo prophylactically.

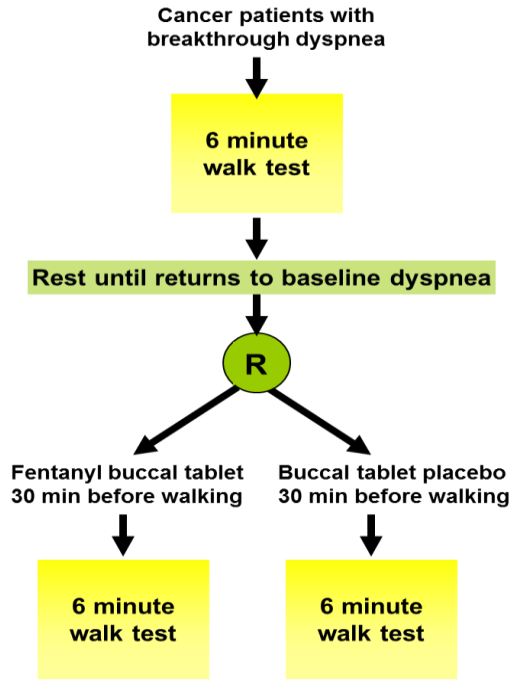

Figure 1. Study Flow Chart

Based on our experience conducting symptom control trials, this study will take each patient approximately 1 hour to complete in a single visit. We believe this study design is feasible and would not add undue burden for patients. Patients will be compensated with a $50 gift card for their time and effort.

C.2. Eligibility Criteria. The eligibility criteria are shown in Table 2.

Table 2. Study Eligibility Criteria

Inclusion Criteria

1. Diagnosis of cancer with evidence of active disease
2. Breakthrough dyspnea, defined in this study as dyspnea on exertion with an average intensity level >/=3/10 on the numeric rating scale
3. Outpatient at MD Anderson Cancer Center seen by the Supportive Care Service, Thoracic Medical Oncology or Cardiopulmonary Center
4. Ambulatory and able to walk with or without walking aid
5. On strong opioids with morphine equivalent daily dose of 60-130 mg for at least one week, with stable (i.e. +/- 30%) regular dose over the last 24 hours
6. Karnofsky performance status >/=50%
7. Age 18 or older
8. Able to complete study assessments
9. Must speak and understand English.

Exclusion Criteria

1. Dyspnea at rest >/=7/10 at the time of enrollment
2. Supplemental oxygen requirement >6 L per minute
3. Delirium (i.e. Memorial delirium rating scale >13)
4. History of unstable angina or myocardial infarction 1 month prior to study enrollment
5. Resting heart rate >120 at the time of study enrollment
6. Systolic pressure >180 mmHg or diastolic pressure >100 mmHg at the time of study enrollment
7. History of active opioid abuse within the past 12 months
8. History of allergy to fentanyl
9. Severe anemia (Hb <7g/L) if documented in the last month and not corrected prior to study enrollment*
10. Bilirubin >5x Upper limit of normal if documented in the last month and not lowered to <5x normal prior to study enrollment*
11. Diagnosis of acute pulmonary embolism within past 2 weeks
12. Diagnosis of pulmonary hypertension
13. Unwilling to provide informed consent

* To minimize study burden for participation in this 2 hour study, extra bloodwork will not be drawn unless the patient already has the above lab abnormalities documented and need to be corrected.

C.3. Study screening. A 2 step consent process will be used. First, a verbal consent will be obtained by the study staff to proceed with screening of potential participants for eligibility and to characterize their dyspnea using the dyspnea survey and the cancer dyspnea scale. Outpatients may be contacted by phone within 1 week prior to their scheduled clinic visit to inform them of this study so they can make necessary arrangements if interested in participating. Eligible patients will then be formally enrolled onto the study after they have signed the informed consent indicating a willingness to participate in the trial. The number of patients screened, approached, eligible, and enrolled will be documented. Reasons for refusal for eligible patients will also be captured.

C.4. Randomization. Randomization and Trial Conduct. Patient randomization will be conducted through the Clinical Trial Conduct website https://biostatistics.mdanderson.org/ClinicalTrialConduct), which is maintained by the Department of Biostatistics at MD Anderson Cancer Center. The trial statistician will train the users (pharmacists or research nurses) in the use of this website for randomizing patients. The methodology to replace a patient in CTC is as follows: Edit the patient to be replaced modifying MRN and the stratification factor. Then add a history of the changes made to the Notes section. Randomization will be 1:1 between

the placebo and treatment arms, and stratified by baseline level of dyspnea NRS at rest at the time of enrollment (i.e. 0-3, 4-6).

C.5. Blinding. Both the patient and the research staff conducting the assessment will be blinded to the treatment assignment. FBT will be dispensed by Dispensing Pharmacy at MD Anderson. Identically appearing placebo is not available from the manufacturer. Thus, placebo will be produced by a compounding pharmacy, and will be similar in appearance to FBT. Both the patient and the research staff conducting the assessments will be blinded to the nature of the intervention. Further to that, we will check the blinding from patients and study staff at the end of study.

C.6. Research staff. An orientation will be held with research staff involved in this study to introduce them with the study design and to standardize the provision of each intervention.

C.7. Study Interventions. The supply of study medication (both FBT and placebo) will be provided by Teva Pharmaceutical Industries Ltd. FBT was FDA approved (NDA 021947) in 2006 for "the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain." Immediately upon patient enrollment, the study physician will be notified and will determine the morphine equivalent daily dose (MEDD) in real time using standardized equianalgesic ratios. Based on clinical practice and similarly to the dose used for breakthrough pain, we will use an FBT dose equivalent to 20-50% of the MEDD (Table 3). For patients randomized to receive FBT, the study medication will be provided by Dispensing Pharmacy and will then be administered 30 minutes before the second 6-minute walk test. We estimated the FBT dose based on the following assumptions:

- A single rescue dose of 25-50% of the MEDD is safe and effective for relief of dyspnea (Bruera *et al.* 1993, Charles *et al.* 2008, Mercadante *et al.* 2012).
- Fentanyl buccal tablet has approximately 65% oral bioavailability (Darwish *et al.* 2007).

Table 3. Dose of Fentanyl Buccal Tablet Based on Morphine Equivalent Daily Dose

Morphine equivalent daily dose (mg)	FBT dose (mcg)[a]	Number of FBT tablets	Number of placebo tablets
60-65	100	1 x 100 mcg	1
66-130	200	2 x 100 mcg	2

Abbreviations: FBT, fentanyl buccal tablet
[a] FBT is available in 100 mcg and 200 mcg strengths.

Instructions for taking study medication: Once the tablet is removed from the envelope, the patient should immediately place the entire tablet in the buccal cavity (above a rear molar, between the upper cheek and gum). Patients should not split the tablet. The FBT

tablet should not be sucked, chewed, or swallowed, as this will result in lower plasma concentrations than when taken as directed. The FBT tablet should be left between the cheek and gum until it has disintegrated, which usually takes approximately 14-25 minutes. After 30 minutes, if remnants from the tablet remain, they may be swallowed with a glass of water.

Both the patient and the research staff conducting the assessments will be blinded to the nature of the intervention. During this entire study, patients will be monitored closely by trained research staff, and will have rapid access to medical care if needed. Because this involves only a one-time dose given to opioid tolerant patients, and under close monitoring by trained staff, we believe the dosing schedule proposed is safe. As a precautionary measure, patients will be asked to wait for 4 hours after the last walk before driving or operating heavy machinery.

C.8. Medication use during study. To minimize the co-intervention effect on dyspnea, patients will be advised to avoid using breakthrough opioids (for any reason) or bronchodilators for at least 2 hours prior to and during the study.

C.9. The 6-minute walk tests will be conducted based on guidelines from the American Thoracic Society (Laboratories 2002). The research staff conducting the walk test must be certified in cardiopulmonary resuscitation with a minimum of Basic Life Support by an American Health Association–approved cardiopulmonary resuscitation course. Walking aid and supplemental oxygen via nasal prongs are allowed as long as patients keep them the same as before enrollment and during the entire study. This walking test allows patients to rest if they need to, and is highly acceptable to patients. It provides important information regarding patients' functional status, exercise capacity, and health-related quality of life (Guyatt *et al.* 1985, Guyatt *et al.* 1985). Before and after each test, we will be assessing the (1) dyspnea and fatigue level with numeric rating scale and Borg scale, and the (2) respiratory rate and oxygen saturation. After each test, we will also be assessing (1) the distance walked at the end of each minute or portion of, (2) the total walking time, (3) the level of dyspnea at the end of each minute or portion of (NRS and Borg scale), and (4) the average walking speed.

The 6-minute walk test has excellent short term reproducibility (Guyatt *et al.* 1985), as well as good face, construct, and predictive validity (Du Bois *et al.* 2011), and changes in this test are concordant with changes in symptoms and mortality (Olsson *et al.* 2005). The minimal clinical significant difference is found to be 24-45 m for patients with idiopathic pulmonary fibrosis (Du Bois *et al.* 2011), and 86 m for patients with COPD.

The first 6-minute walk test was designed to provide important information regarding a patient's level of dyspnea on exertion, and to facilitate intra-individual comparison since there is significant variability in the expression of dyspnea among patients.

C.10. Variable rest period. After the first and second 6 minute walk test, patients will be asked to sit down and rest. How long they rest would depend on when they return to baseline level of dyspnea numeric rating score + 1 or below (e.g. if baseline dyspnea = 4, they need to return to a level of 5 or less to qualify for next stage). During this rest

period, patients will be assessed every 5 minutes to check their dyspnea level. If their dyspnea level met criteria and they feel ready to walk again, they will be given the study treatment and asked to wait for 30 minutes before they do the second walk.

C.11. Stopping rules. Patients who do not develop any increase from their baseline dyspnea after the first 6-minute walk will not proceed to the next stage because of the lack of exercise-induced dyspnea. If at any time during the study patients develop chest pain, severe leg cramps, staggering, diaphoresis, and/or dizziness, they will be asked to stop the study. If patients require more than 1 hour of rest and their dyspnea level still has not returned to baseline, they will also be taken off study. Patient dropouts and walk test failures prior to the administration of drug or placebo will be replaced.

C.12. Study assessments. See Table 4 for a detailed description of all study assessments.

Table 4. Summary of Study Assessments

Assessments	Baseline	After 1st 6 min walk test	Rest Period	Before 2nd 6 min walk test	After 2nd 6 min walk test
Demographics and cancer diagnosis[1]	✓				
Medication history[2]	✓				
Karnofsky performance status, spirometry testing[1]	✓				
Edmonton Symptom Assessment Scale[4]	✓				
Dyspnea Survey[5]	✓				
Cancer Dyspnea Scale[6]	✓				
O_2 saturation, blood pressure, heart rate and respiratory rate	✓	✓		✓	✓
Dyspnea Numeric Rating Scale[7]	✓	✓	✓	✓	✓
Dyspnea Borg scale/Fatigue Borg scale[8]	✓	✓		✓	✓
Walking test parameters[9]		✓			✓
Adverse effects[10]				✓	✓
Neurocognitive testing[11]		✓			✓
Global assessment, study satisfaction and blinding[12]					✓

[1] patient initials, medical record number, date of birth, sex, race/ethnicity, education, marital status, cancer diagnosis, co-morbidities, cause(s) of dyspnea, C-A-G-E, Karnofsky Performance Status, height/weight and spirometry.
[2] medications that could be used to treat dyspnea, including scheduled and as needed opioids, bronchodilators, steroids, and supplemental oxygen will be documented.
[3] an 11-point assessment scale that rates patients' functional status between 0% (death) and 100% (completely asymptomatic) based on their ambulation, activity level, and disease severity (Schag *et al.* 1984).
[4] validated questionnaire that measures 10 common symptoms in the past 24 hours (pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, sleep, and feeling of well-being) using numeric rating scales (Bruera *et al.* 1991). It also includes two additional questions about financial and spiritual distress.
[5] characterization of patients dyspnea including the following: presence of dyspnea at rest, average dyspnea in last 24 hours, worse dyspnea in last 24 hours, best dyspnea in last 24 hours, number of episodes of exacerbation per day, triggers of breakthrough dyspnea, average

duration of each episode, current treatment for breakthrough dyspnea. It also includes two additional questions about financial and spiritual distress.
[6] validated 12-item questionnaire specifically designed to assess the quality of dyspnea in cancer patients during the past few days (Tanaka *et al.* 2000). Each item has a score between 1 and 5, for a maximum of 60. There are sub-scores for sense of effort, anxiety, and discomfort.
[7] a 0 (no dyspnea) to 10 (worst dyspnea) categorical scale validated for rating the severity of dyspnea (Dorman *et al.* 2007, Gift and Narsavage 1998, Powers and Bennett 1999). We will be measuring it every minute during the 6 minute walk test at 0, 1 min, 2 min, 3 min, 4 min, 5 min and 6 min (or end of walk).
[8] a 0 to 10 categorical scale for rating the severity of dyspnea and fatigue. It is a ratio scale with descriptive anchors throughout the range in which a rating of 8 signifies breathlessness twice as severe as 4, which in turn is twice as severe as 2 (Dorman *et al.* 2007, Gift and Narsavage 1998, Kendrick *et al.* 2000, Powers and Bennett 1999).
[9] include the total distance walked, total walking time, the distance and time of first rest due to dyspnea, average walking speed.
[10] adverse effects related to the use of FBT, such as dizziness, drowsiness, nausea, and itching will be assessed using a numeric rating scale from 0-10.
[11] patients will be asked to do finger tapping 10 and 30 sec, arithmetic, reverse memory of digits, and visual memory). This has been used in other studies by our group.(Bruera *et al.* 1992)[12] patients will be asked about their dyspnea (worse, about the same, or better) comparing between the level of dyspnea between the first and second 6-minute walk tests (Guyatt *et al.* 1993, Redelmeier *et al.* 1996). Study satisfaction will be assessed with the following questions, “Was it worthwhile for you to participate in this research study?”, “If you had to do it over, would you participate in this research study again?”, “Would you recommend participating in this research study to others?”, “Did you quality of life get better by participating in this research study?”, “Did you quality of life get worse by participating in this research study?” Blinding will be assess by asking patients and study staff which group assignment they believe they received: “FBT”, “placebo”, or “do not know”.

C.13. Feasibility data. In addition to clinical outcomes, we will also collect feasibility data in this study, including the following:

- Rates of recruitment and retention (% of subjects able to complete the study)
- Reasons for refusal and dropout
- Outcome measure—we will compare the sensitivity of Numeric rating scale and Borg scale to change, and identify key measure for future study
- Participant satisfaction—participants will provide an opinion regarding their satisfaction with study overall

C.14. Patient Safety, Monitoring, and Confidentiality. During the study, trained research staff will be performing study assessments and monitoring the patients carefully throughout the study period. If a patient desaturated at the end of the walk (<90%), we will put her on oxygen and consider a referral to cardiopulmonary center. A study physician will also be available by pager to address any concerns, distress, or questions, and will attend to the patient as needed. Patients will be doing the test in a hallway outside the Supportive Care Center which typically does not have a lot of traffic, and will have immediate access to medical and nursing care if needed. See stopping

rules above for further details. With the planned doses of fentanyl in opioid-tolerant patients, we do not expect any significant side effects.

Regulatory monitoring will be provided by the principal investigator, the Institutional Review Board (IRB), and the Data Safety and Monitoring Board (DSMB). Patient confidentiality will be ensured by use of study numbers, secure storage of clinical data, and anonymous reporting.

D. Statistical Analysis

D.1. Power Calculation. The sample size of 20 patients is determined by sponsor funding for this research. To account for replacements, we will ask for the maximum sample size to be 25.

The primary objective of determining effect size for powering future studies is simply a matter of collecting data on the distributional properties of dyspnea scores for the two arms. We do not expect the variances of the differences within placebo and treatment to be equal based on preliminary results of a recent similar study. Therefore for proper sample size calculations a placebo arm is necessary. We base our estimates on our other similar study, in which we observed a standard deviation for the difference within treatment arm of approximately 2.0 and a standard deviation for the difference within placebo arm of approximately 3.0. 10 patients will provide a 95% CI for the standard deviation of the difference within placebo of (2.1, 5.5). 10 patients will provide a 95% CI for the standard deviation of the difference within treatment of (1.4, 3.7). [NCSS PASS 2005 – Helps and Aids – Standard Deviation Estimator]

For the secondary objectives, 10 evaluable patients in the FBT arm provides 80% power to detect an effect size as small as 1.0 when alpha=5% using a two-sided paired t-test to compare dyspnea between the first and second walk tests.

D.2. Data Analysis. Summary descriptive statistics will be provided for demographics, outcomes, and other collected variables and will include proportions, medians, means, 95% confidence intervals, and other simple statistics as appropriate for the measure.

Patients who started but failed to complete the 2nd walk test will not be replaced; instead they will be included in the analysis and treated as fully evaluable patients. If we are able to collect a final dyspnea score from such patients then we will use that score along with the distance walked to failure as their values for analysis. Should we be unable to collect the final dyspnea score, we will assign that patient a dyspnea value equal to the maximal score on the dyspnea assessment along with a distance walked to the point of failure. Patient dropouts and walk test failures prior to starting the second walk test will be replaced.

Comparisons within arms (1st secondary objective) will be performed using multiple linear regression based on the difference of the final dyspnea scores of the first and second walk tests. We will include baseline dyspnea and distance walked as

covariates. Size and significance of the difference in dyspnea will be determined by examination of the intercept.

Comparisons between arms (2nd secondary objective) will be performed to determine if treatment is different from placebo for exercise induced dyspnea, walk distance, neurocognitive function and various physiological parameters. Each endpoint will be evaluated at the end of the 2nd walk test. Analysis method will be linear regression of placebo vs fentanyl adjusted for the baseline value of the endpoint being evaluated.

It is understood that 10 or 20 patients is too few for a proper analysis of linear regression with more than one factor. All hypothesis tests for this study are purely exploratory. The type I error rate will be 5% for each comparison.

E. Data Confidentiality Procedures

Health information will be protected and we will maintain the confidentiality of the data obtained from the patient's chart.

Collection of identifiers: We will collect and securely store patients' identifiers (including name, medical record number, and demographic specifications). Each patient will be assigned a study number that will be the only identifier to figure in the analytical file and personal data will not be disclosed in any form. The key linking these numbers will be retained in a securely locked file by the investigator.

Data Storage: Protection of electronic and paper records will be guaranteed. All electronic records will be stored on password-protected institution computers behind the institution firewall. Any paper records will be classified and stored in locked files inside a locked office.

Training of personnel: Only MDACC personnel trained in maintaining confidentiality, the principal investigator, co-investigators, and research staff will have access to study records.

Data sharing: Study data will not be shared with any individuals or entities without prior IRB approval. The data will be kept by the principal investigator in a locked file cabinet and password protected computer behind the institution firewall.

Final disposition of study records: PHI may be maintained indefinitely, aggregated in the future, and used for future research studies.

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