The effect of preoperative and postoperative incentive spirometry in patients undergoing major abdominal surgery

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Study Device(s): **MIR Spirobank G**
ZephyrX

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Protocol Revision History

Initial Approval Version	**30 April 2021**
Amendment #1 Version	**06 April 2022**

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

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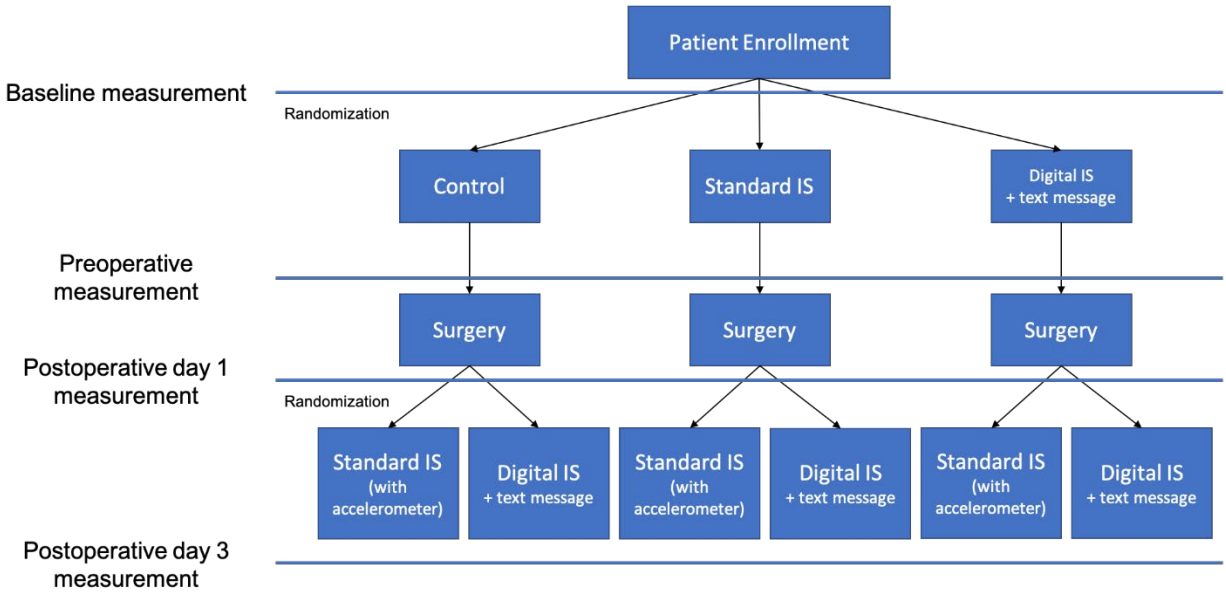
PROTOCOL SUMMARY

Synopsis

Title:	The effect of preoperative and postoperative incentive spirometry (IS) in patients undergoing major abdominal surgery
Study Description:	The goal of this study is to determine the efficacy of incentive spirometry (IS) to improve pulmonary function in the preoperative and postoperative surgical setting. We hypothesize that IS will improve pulmonary function for patients undergoing major abdominal surgery when controlling for protocol compliance. Additionally, we hypothesize that a digital IS device enabled with a text message-based mobile health intervention will improve pulmonary pre-habilitation and rehabilitation, as well as postoperative compliance with the IS device.
Objectives:	Primary Objective: To determine the efficacy of incentive spirometry to improve FEV1 in the preoperative surgical setting. Secondary Objectives: 1. To determine the efficacy of incentive spirometry to improve FVC and pulse oximetry in the preoperative surgical setting. 2. To determine the change in FEV1, FVC and pulse oximetry after surgery. Exploratory Objectives: 1. To determine the daily number of times patients perform incentive spirometry in the preoperative and postoperative setting. 2. To determine whether standard incentive spirometers move throughout a patients' postoperative stay using accelerometers, as a proxy for how often patient uses the device. 3. To evaluate whether a digital IS device + text message based mobile health intervention will improve FEV1, FVC, and pulse oximetry compared to standard IS. 4. To evaluate the rate of pulmonary complications across the 3 preoperative groups.
Endpoints:	Primary Endpoint: Change in FEV1 at day-of-surgery preoperative from baseline Secondary Endpoints: 1. Change in FVC and pulse oximetry at day-of-surgery preoperative from baseline 2. Change in FEV1, FVC and pulse oximetry at postoperative day 3 from day 1

	Exploratory Endpoints: 1. Daily frequency of digital IS use. 2. Movement data of standard IS with accelerometers (this is a proxy endpoint for IS use). 3. Difference in changes in FEV1, FVC, and pulse oximetry between randomized groups. 4. Postoperative complications defined by Modified Accordion Grading System (MAGS)
Study Population:	We plan to enroll 156 adult patients who are scheduled to undergo major abdominal surgery with an expected postoperative hospital stay of $\geq$ 48 hours.
Phase:	N/A
Description of Sites / Facilities Enrolling:	The study will take place at Barnes Jewish Hospital system/Washington University School of Medicine.
Description of Study Intervention:	Patients will be randomized into 3 groups: (1) control group with no IS, (2) standard IS, and (3) digital IS + text message. Groups 2 and 3 will be instructed to perform spirometry every day for at least 7 days prior to surgery. FEV1, FVC, and pulse oximetry will be obtained for all patients at 4 different time points: (1) baseline measurement at the time of enrollment, (2) preoperatively on the day of surgery, (3) immediate postoperative period 24 hours after surgery, and (4) delayed postoperative period on postoperative day 3. After surgery, patients are re-randomized to conventional spirometry (which is standard of care) or digital spirometry. The digital spirometer couples with a HIPAA-compliant mobile app which stores data and shares it with the research team via the HIPAA-compliant dashboard. These data will be used to assess compliance with the intervention for the digital group both in the preoperative and postoperative period. Sustained accelerometer movement data will be used as a surrogate for frequency of use and will be used to assess compliance with the intervention for the standard group in the postoperative period.
Study Duration:	Approximately 1000 major abdominal surgeries take place at our institution yearly. The rate-limiting step for enrollment is going to be the digital IS devices, which we plan to re-use. Purchasing 20-30 devices for 150 patients, we anticipate completing accrual in 12 months. (Note that all patients receive an individualized spirometry mouthpiece; only the digital device that does not come into contact with patient is re-used.) We anticipate data analysis will be completed 6 months following closure to accrual.
Participant Duration:	Approximately 1 month

SCHEMA


Patient Enrollment
Baseline measurement
Randomization
Control
Standard IS
Digital IS
+ text message
Preoperative
measurement
Surgery
Surgery
Surgery
Postoperative day 1
measurement
Randomization
Standard IS
(with
accelerometer)
Digital IS
+ text message
Standard IS
(with
accelerometer)
Digital IS
+ text message
Standard IS
(with
accelerometer)
Digital IS
+ text message
Postoperative day 3
measurement

SCHEDULE OF ACTIVITIES

	Baseline/Enrollment	Pre-operative Days 1-7	Day of surgery	Post-operative Day 1	Post-operative Day 3
Consent[1]	X				
Randomization[2]	X				
Re-randomization[3]				X	
Spirometry intervention		X[5]		X	X
FEV1, FVC, pulse oximetry	X		X[4]	X	X
Assess for AE/Complications	X	X	X	X	X

Notes:

1. Consent should take place not less than 8 days prior to surgery.
2. Patients will be randomized into three groups: (1) control group with no IS, (2) standard IS, and (3) digital IS + text message.
3. Following surgery, patients will be re-randomized into two groups: (1) standard IS, and (2) digital IS + text message.
4. Measurement of PFTs and pulse oximetry should be obtained prior to surgery on the day of surgery.
5. For groups 2 and 3 only.

1.0 INTRODUCTION

1.1 Background/Rationale

Recent developments in perioperative care, like the development of enhanced recovery pathways, have been designed to decrease practice variability and achieve early recovery after surgery to decrease the postoperative length of hospitalization for patients.[1-5] Despite this, there has not been a significant reduction in postoperative readmissions.[6-8] The complication rate after major abdominal surgery such as pancreaticoduodenectomy and liver resection continues to be up to 50%.[8-10] Most research aiming to improve postoperative outcomes has focused on postoperative interventions, but in the last couple of years, there has been significant interest in developing interventions that address the preoperative period.[11-18] One specific intervention that has been proposed with limited and variant support is the use of incentive spirometry (IS). IS involves using a device to facilitate deep breathing exercises to increase lung capacity and open airways with the goal to prevent pulmonary complications.[19-23]

IS has had widespread implementation in the United States in the **postoperative** period although there is limited data supporting its efficacy in clinical trials. A systematic review by Overend et al. evaluated 46 studies to ascertain the effect of postoperative IS on the incidence of postoperative complications, but failed to show a positive effect for postoperative IS.[24] More recently, Zoremba et al. evaluated the effect of IS in the postoperative recovery unit on lung function for obese patients undergoing a variety of non-abdominal surgical procedures.[25] They did not find significant differences in pulse oximetry and pulmonary function tests (PFTs) immediately after surgery, but at all subsequent time points—1, 2, 6, and 24 hrs after surgery—SpO2, FVC, FEV1 and PEF were higher for the IS group. In summary, data regarding postoperative IS use is sparse and inconsistent.

There is emerging field of study to evaluating IS in the **preoperative** setting which have yielded mixed results.[23,26,27] A 2010 study from Kundra et al. evaluated the effect of preoperative IS on patients undergoing laparoscopic cholecystectomy and failed to show any differences in preoperative PFTs compared to baseline in the control group, while patients in the intervention group had a 11.9% increase in FEV1 and 12.1% increase in FVC compared to baseline.[28] Additionally, Fulop et al evaluated the use of IS 4-5 times daily before undergoing colorectal surgery in which the intervention group had improved inspiratory capacity compared to baseline, compared to the control group in which the inspiratory capacity remained the same (113% vs 100% of baseline value).[29] Similarly, a group from India reported their results of preoperative IS regiment consisting of 15 mins of IS every 4 hrs for 7 days before surgery, compared to standard of care.[30] Preoperative control peak expiratory flow rate (PEFR) was not different between groups, and postoperatively they only found a statistically significant difference on postoperative day

2 (69.48% intervention vs 61.66% control of baseline PEFR). In all the preoperative studies there was no statistically significant differences in postoperative morbidity and mortality.

In summary, there is a significant knowledge gap and methodological concerns regarding the benefits of IS use across the continuum of surgical care. As reported above, there is a substantial variance in IS specific measurements and outcomes evaluated across many surgical studies in the preoperative and postoperative period. An important, and unaddressed, methodological issue with the current data available is the lack (and unreported) data pertaining to the compliance of patients using the IS as intended.[23] Most protocols reported in the literature detail the patient IS instructions/protocol ranging from IS use at 4-5 times per a day up to 10 times per hour but fail to objectively evaluate and adjust their analyses to patients successful completing the IS protocol. [31-33]

To overcome the methodological problems recent technologies have emerged that can accurately track IS use and could be used to address this limitation. ZEPHYRx® has developed a **1) digital Bluetooth-enabled IS** that allows for the continuous and objective remote monitoring of patient compliance with pre- and postoperative IS via a smartphone app and online provider dashboard. New research has suggested that mobile health based interventions can be used successfully to change patient behavior. If coupled with ZEPHYRx® technology, these could be used to increase patient compliance with IS.[34-38] They have also developed **2) accelerometer implanted standard IS devices**; which utilizes an accelerometer to monitor movement of the IS device as a proxy for IS use using standard non-Bluetooth enabled IS devices.

1.2 Study Design

The goal of this study is to determine the efficacy of IS to improve pulmonary function in the preoperative and postoperative surgical setting. We hypothesize that IS will improve pulmonary function for patients undergoing major abdominal surgery when controlling for protocol compliance. Additionally, we hypothesize that a digital IS device + text message based mobile health intervention will improve pulmonary pre-habilitation and rehabilitation, as well as postoperative compliance with the IS device.

2.0 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints	Justification for Endpoints
Primary		
To determine the efficacy of incentive spirometry to improve FEV1 in the preoperative surgical setting.	Change in FEV1 at day-of-surgery preoperative from baseline	

Secondary		
3. To determine the efficacy of incentive spirometry to improve FVC and pulse oximetry in the preoperative surgical setting. 4. To determine the change in FEV1, FVC and pulse oximetry after surgery.	1. Change in FVC and pulse oximetry at day-of-surgery preoperative from baseline 2. Change in FEV1, FVC and pulse oximetry at postoperative day 3 from day 1	
Tertiary/Exploratory		
1. To determine the number of times patients perform incentive spirometry in the preoperative and postoperative setting. 2. To determine whether standard incentive spirometers move throughout a patients' postoperative stay using accelerometers, as a proxy for how often patient uses the device.. 3. To evaluate whether a digital IS device + text message based mobile health intervention will improve FEV1, FVC, and pulse oximetry compared to standard IS. 4. To evaluate the rate of pulmonary complications across all 6 groups.	1. Daily frequency of IS use 2. Postoperative complications defined by Modified Accordion Grading System (MAGS)	

3.0 STUDY POPULATION

3.1 Inclusion Criteria

1. Patients scheduled to undergo major abdominal surgery with expected postoperative length of stay of 48 hours or more.

2. Access to a smartphone.

3. At least 18 years of age.

4. Ability to understand and willingness to sign an IRB approved written informed consent document.

3.2 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed

1. The registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

4.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomized to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials

(CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (if applicable).

5.0 STUDY PROCEDURES

After enrolling in the study, patients will be randomized pre-operatively into one of the following 3 groups: (1) control group with no IS, (2) standard IS, and (3) digital IS + text message (see schema). Baseline PFTs and pulse oximetry on room air will be obtained for all patients.

Patients in the control group will not receive a spirometer for preoperative use, which is current standard of care. Patients in the standard group will receive a conventional spirometer; they will receive instruction on how to perform spirometry correctly and will be asked to perform spirometry 30 times a day, as per the Washington University Surgical Prehabilitation and Readiness Program (SPAR) protocol. Patients in the digital group will receive an FDA-approved, Bluetooth digital spirometer (Spirobank G) that is compatible with health monitoring software developed by ZEPHYRx®. All patients receive an individual mouthpiece in which to breathe. The digital devices that are separate from but attached to the mouthpiece may be re-used. These will be thoroughly cleaned between patients. The digital spirometer couples with a HIPAA-compliant mobile application that calculates and stores PFT results. The research team will have access to the data via the ZEPHYRx® provider dashboard. Patients in the digital spirometer group will receive the same instruction as the patients in the standard IS group and asked to follow the same preoperative IS protocol. Absence of spirometry for 24 hours will trigger a text message reminder to encourage compliance with IS.

On the day of surgery, PFTs and pulse oximetry on room air will be recorded for all patients in the preoperative area. After surgery, all patients will receive a spirometer as is standard of care. On postoperative day 1, patients will be re-randomized. Those in the standard group will receive a standard spirometer for postoperative use, whereas patients in the digital group will obtain a digital spirometer (Spirobank G + ZEPHYRx®-enabled). All patients will receive instruction on how to perform spirometry and will be instructed to perform spirometry 10 times per hour, every hour while awake as is current practice for the department of surgery. The conventional spirometer will be equipped with an accelerometer that will allow the research team to determine whether the spirometer moves throughout the patients' postoperative stay (as a proxy for IS use) in the standard group. Compliance amongst the digital group will be determined using the ZEPHYRx® dashboard as described above. Just as in the preoperative period, the digital group will receive text reminders to perform spirometry if they do not perform spirometry in a 24-

hour period. PFTs and pulse oximetry on room air will be obtained on postoperative day 1 and postoperative day 3. The clinical inpatient team will be blinded to compliance data.

After obtaining final measurements on postoperative day 3, the study will conclude, and the spirometers will be collected. Postoperative outcomes data, including perioperative mortality postoperative complications, length of stay, and need for readmission, will be collected for all patients as per protocol for the Division of Hepatobiliary Surgery.

5.1 Definitions of Evaluability

All patients who are initially randomized are evaluable for the primary endpoint. Patients are evaluated from first enrollment through post-operative day 3.

6.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below.

Adverse events will be tracked from start of spirometry intervention through post-operative day 3. All adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF
- Any adverse events related to presenting diagnosis or surgery
- Any adverse events determined unrelated to spirometry

6.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

6.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI (or designee) is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

7.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form Medical History Form	At enrollment/baseline
PFT + pulse oximetry	Baseline, preoperatively on day of surgery, post-op day 1, post-op day 3
Surgery form	Day of surgery (+1 week)
Follow-up Form	1 month post-op
AE log	Continuous

8.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least one patient has been enrolled) or one year after accrual has opened (if no patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy

- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design

This is a prospective, single-center, randomized trial. The enrolled patients will be randomized 1:1:1 to one of three groups: control, standard IS, and digital IS + text message. They will have baseline measurement at the time of randomization, and pre-operative measurement after randomization and before the surgery. After surgery, patients will be re-randomized to either standard IS or digital IS + text message. Measurements at post-op days 1 and 3 will be taken. The primary objective of this study is to determine the efficacy of incentive spirometry to improve FEV1 in the preoperative setting. The secondary objectives are to determine the efficacy of incentive spirometry to improve FVC and pulse oximetry in the preoperative setting, and FEV1, FVC, and pulse oximetry in the postoperative setting. The exploratory objectives are to determine the daily number of times patients perform incentive spirometry in the postoperative setting and evaluate the rate of pulmonary complications across the 3 preoperative groups.

9.2 Randomization

A computer-generated randomization scheme with various block sizes will be used to assign patients. It is maintained centrally by the study statistician. After enrollment in the study and obtaining consent, randomization will take place in REDCap.

9.3 Data Collection

FEV1, FVC, and pulse oximetry will be obtained for all patients at 4 different time points: (1) baseline measurement at the time of enrollment; (2) preoperatively on the day of surgery; (3) immediate postoperative period 24 hrs after surgery; and (4) delayed postoperative period on postoperative day 3. The digital spirometer couples with a HIPAA-compliant mobile app which stores data and shares it with the research team via a HIPAA-compliant dashboard. These data will be used to assess compliance with the intervention for the digital group both in the preoperative and postoperative period. Sustained accelerometer movement data will be used as a surrogate for frequency of use and will be

used to assess compliance with the intervention for the standard group in the postoperative period.

9.4 Endpoints

The primary endpoint is FEV1 change at day-of-surgery preoperative from baseline. The secondary endpoints include FVC and pulse oximetry change at day-of-surgery preoperative from baseline, change in FEV1, FVC and pulse oximetry at preoperative day 3 from day 1. Exploratory Endpoints are daily frequency of IS use and postoperative complications defined my Modified Accordion Grading System (MAGS).[39]

9.5 Sample Size/Power Analysis

The sample size calculation is based on the primary outcome only. Previous research has shown that the mean difference in FEV1 between control and preoperative incentive spirometry intervention groups is 0.4 L with a standard deviation of 0.6.[28] Bonferroni correction will be used for three-group comparisons. Sample sizes of 49 per group achieve 80.6% power to detect the difference in FEV1 assuming a mean difference of 0.4 L and a standard deviation of 0.6 at a significance level of 0.017 using a two-sided, two-sample, equal-variance t-test. To account for a 5% dropout rate, we will enroll 52 patients per group for a total of 156 patients enrolled in the study.

9.6 Data Analysis

The analysis will be intent-to-treat approach. The FEV1, FVC and pulse oximetry changes at day-of-surgery preoperative from baseline will be compared across three groups using ANOVA or Kruskal-Wallis test, as appropriate. The linear regression model will be considered to adjust for the other interested variables including age, sex, smoking status, BMI, ASA, and malignancy. The same analysis method will be conducted for FEV1, FVC and pulse oximetry changes at preoperative day 3 from day 1. The frequency of use, defined as the daily number of times patients perform incentive spirometry, will be compared across all groups in the postoperative setting using ANOVA or Kruskal-Wallis test, as appropriate. For postoperative complications, Chi-square test will be used to test the differences between six groups. The univariate logistic regression model will estimate the odds ratio of postoperative complication. Multivariate analysis through stepwise selection will be considered to examine the relationship between binary outcome and independent predictors, where a significance level of 0.3 is required to allow a predictor into the model, and a significance level of 0.35 is required for a predictor to stay in the model. All analyses will be conducted using SAS (SAS Institute, Cary, NC) at the two-sided 5% significance level.

10.0 REFERENCES

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