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THESIS PROPOSAL
MASTERS OF INTERNAL MEDICINE
UNIVERSITI KEBANGSAAN MALAYSIA

Impact of Aerobika® Oscillating Positive Expiratory Pressure (OPEP) in Improving Small Airway Disease and COPD Assessment Test (CAT) Score in Chronic Obstructive Pulmonary Disease (COPD) .

FF - 2021-175

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CHAPTER 1

INTRODUCTION

1.1 Research Background

Chronic obstructive pulmonary disease (COPD) is a progressive chronic lung disease that makes breathing difficult with mucus buildup in the inflamed airway [1, 2] and lungs hyperinflation due to expiratory flow limitation. Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as a common, preventable and treatable disease [3] with significant morbidity and mortality, and incurs intensive expenditure of healthcare resources [4]. This disease is currently the fourth leading cause of death in the world but is projected to be the 3rd leading cause of death by 2020. In 2012, global death from COPD accounted about 6% which equal to more than 3 million deaths in world population [3]. The mortality burden of COPD is expected to rise to 8.6% by 2030 [5]. In Malaysia, the prevalence of moderate to severe COPD in Malaysia in 2010 is 4.7% which equals to 448,000 cases [5-7].

COPD is attributed by long-term exposure to noxious particles and toxic gases [1]. Tobacco smoking is the main cause of COPD globally [8]. The Third National Health and Morbidity Survey (NHMS III) conducted in Malaysia in 2006 showed that the prevalence of male ever smokers was 57.6% and in female is 2.5% [9]. Other than that, inhalation of organic or chemical dust and fumes, and biomass exposure also among the risk factors of COPD. Exposure to noxious particles will cause activation of inflammatory immune responses. However, continuous and repetitive exposure towards these noxious particles will lead to tissue remodelling in small airways causing smooth muscle hypertrophy and fibrosis causing major site of obstruction in COPD [10].

COPD is characterized by a mixture of small airway disease and parenchymal lung tissue destruction causing emphysema which affecting gas transfer [11]. Small airway is defined as airways of less than 2mm in internal diameter which lacks in cartilage, and have greater proportion of smooth muscles with fewer goblet cells in the epithelial layers [11]. Approximately 10-25% of total airways resistance in healthy lungs is due to the small airways, with their contribution to total airways resistance increasing substantially in COPD. As the small airways are located in the lung periphery, they are not easily evaluable, which can potentially interfere

with the diagnosis (especially at early stages), monitoring, detection of responses to clinical interventions, and prognostic evaluation in COPD [12].

In COPD patients, the small airways represent the key sites of airflow obstruction, and small airway disease (SAD) is considered a functional hallmark of disease [13]. The presence of SAD progressively increases with higher GOLD classifications and it is closely related to the high impact of disease measured by COPD Assessment Test (CAT) questionnaire. Distributions of SAD among COPD patients classified according to GOLD classification. In each of GOLD A, B, C and D class, the prevalence of SAD are 49%, 88%, 61%, and 96% respectively (**Figure 1)** [13]. As presence of SAD is closely related to high impact of disease with CAT score ≥10 , they tend to have more symptoms [13].

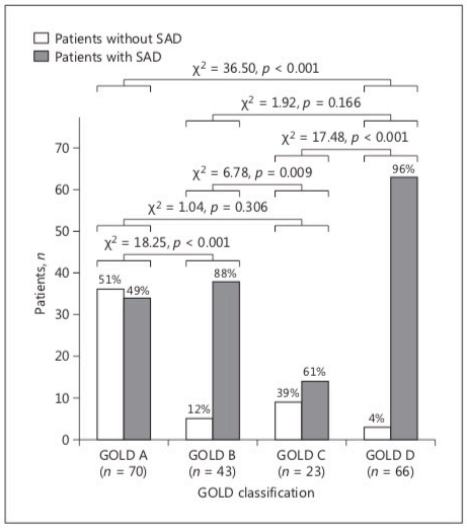


Figure 1: Distribution of patients with and without SAD according to the GOLD classification[13]

1.2 Problem Statement

As mentioned before, in COPD patients, the small airways represent the key sites of airflow obstruction, and SAD is considered a functional hallmark of disease [13]. Spirometry is the most reproducible and objective measurement of airflow limitation [3]. However, it is not sensitive to evaluate SAD. In the context of lung function evaluation, the impulse oscillometry system (IOS), a type of forced oscillation technique, was recently proposed as a better way of detecting SAD than standard spirometry. IOS provides measurement for both proximal and distal airway resistance. In COPD patients, IOS is also useful to detect early phases of disease,

other than useful to assess bronchodilator responsiveness and effect, as well as to define different subgroups of patients according to airflow obstruction. SAD measured by IOS increases progressively according to the severity of disease assessed by GOLD classifications in COPD [13].

The earliest indication of small airways disease when evaluated by spirometry is the deceleration of airflow at the terminal portion of the flow-volume curve, which can be detected by measuring the mean expiratory flow between 25% and 75% of Forced Vital Capacity (FVC) ($FEF_{25-75\%}$). This parameter is calculated by dividing the expiratory volume by the time difference between these two points in the mid-range of the FVC manoeuvre [12]. The use of $FEF_{25-75\%}$/FVC can act as a potential clinical tool for early detection of COPD [12]. Thus, patients who present with low $FEF_{25-75\%}$ values should be monitored closely, as they are susceptible to COPD, even though they may have normal lung function [14].

IOS is a simple, non-invasive method requiring only passive patient cooperation without special manoeuvre for evaluation of lung function through the measurement of both airway resistance and airway reactance.[15] The pressure-flow oscillations are applied at the mouth superimposed on the subject's tidal breaths to measure respiratory system resistance and reactance at different oscillation frequencies. It uses sound waves to rapidly detect airway changes. When analysed, these pressure signals separately quantify the degree of obstruction in the central and peripheral airways [15]. In IOS, it enables measurement of total respiratory resistance (R5) and proximal respiratory resistance (R20), with the R5-R20 difference reflecting small airway resistance [16, 17]. Small airway disease is significance if R5-R20 > 0.71 cmH_2O/L/sec [17-20].

Treatment of COPD requires combination of pharmacological and non-pharmacological approaches. In non-pharmacological treatment, chest physiotherapy and pulmonary rehabilitation is the cornerstone of management of COPD patients. It can result in improvement of symptoms, increased exercise capacity, and improvement in lung functions [21]. By early detection of SAD in COPD, it enables the physician to offer patients with a more targeted approach therapy, for example the use of small particle size inhalers or mechanical intervention for example oscillating positive expiratory device (OPEP), such as Aerobika®.

1.3 Research Question

Can Aerobika® OPEP device improve small airway disease and CAT score in COPD on top of standard therapy.

1.4 Hypothesis

Aerobika® OPEP improves small airway parameters and CAT score on top of standard therapy.

CHAPTER 2

LITERATURE REVIEW

In healthy people, mucociliary clearance and cough mechanisms are normally effective and efficient, but become overloaded if these systems malfunction and in the presence of excessive bronchial secretions. Chest physiotherapy is commonly used to improve the mobilization and removal of airway secretions in patients with respiratory dysfunction [22]. Other non-pharmacological therapy such as active cycle of breathing technique (ACBT) , positive expiratory pressure (PEP), oscillating PEP (OPEP) devices, and intrapulmonary percussive ventilation (IPV) are also known helpful in airway clearance [23]. Techniques may be used alone or in combination with others.

OPEP device has been developed since 1970s , and it was first developed and described in Switzerland, as an adjunct or supplement to traditional airway clearance methods [22, 23]. It has been utilized to promote the clearance of respiratory secretions in individuals with impaired ability to cough, particularly in chronic diseases. It is a hand-held, drug-free medical device that is designed to expand the airways, mobilize mucus, and help to expel mucus from the lungs. It has been shown to improve health-related quality of life and improve lung function in COPD patients [24].

During inhalation of OPEP, it will provide a linear pathway through an inhalation valve. Upon exhalation, a one-way valve within the device mechanism opens and closes intermittently resulting in positive pressure that will hold airways open and sustaining expiratory flow, combines with airway vibrations or oscillations resonating at a frequency similar to the cilia which decrease the viscoelastic properties of the mucus [23, 25-27]. This will thin and help to mobilise sputum, making it easier for removal by deep force exhalations or coughing ("huffing") techniques (**Figure 2**) [23].There are few models of OPEP devices, for example Aerobika® (Trudell Medical International), Acapella® (Smiths Medical), Flutter® (Axcan Scandipharm), Lung Flute® (Medical Acoustics), and Quake® (Thayer Medical).

The Aerobika® OPEP device has been reported to improve symptoms and quality of life outcomes for COPD patients with mucus hypersecretion. This compares the responder rates from two separate studies using the same device, one with the St George's Respiratory Questionnaire (SGRQ) and the other with the CAT score. First study done by Svenningsen et.

al. in 2016 is a randomized cross-over study in 27 COPD patients for 3-4 weeks, used the SGRQ. In their study, the mean SGRQ value for the 14 COPD patients with chronic bronchitis significantly improved from 49 to 40 ($p = 0.01$, paired t-test) following OPEP therapy. SGRQ is a standardized self-administered airways disease-specific questionnaire that divided into three subscales: symptoms, activity, and impacts. Overall, SGRQ is interpreted as quality of life scores [25]. Second study by Sugett J. is a clinical assessment of 37 COPD patients over an 8-week period, used the CAT score. In this study, the mean CAT value for the 26 COPD patients with chronic bronchitis significantly improved from 19.7 to 17.4 ($p = 0.01$, paired t-test) following OPEP therapy. Even though using different validated questionnaire instruments, the results from these two separate studies show good agreement, with nearly two thirds of COPD patients with chronic bronchitis exhibiting clinically significant improvements. In terms of responder rate analysis, Aerobika® OPEP showed significant improvement in symptoms and quality of life greater than the Minimum Clinically Important Difference (MCID), where it proved 64% improvement in SGRQ (MCID ≥ 4) and 62% improvement in CAT score (MCID ≥ 2). [28] MCID is the smallest change in score that patients perceive as beneficial or detrimental, and is useful to aid the clinical interpretation of health status data, particularly in response to intervention. The most reliable estimate of the MCID for SGRQ is 4 points [29], whereas of the CAT score is 2 points. [30]

It is postulated that OPEP will help to increase exercise capacity in COPD patients. In a study done by Nicolini and colleagues in 2018, patients involved in the study were given Lung Flute® OPEP. In their study, OPEP users demonstrated improvement in exercise capacity measured by using 6 minutes walking test (6MWT) compared to control group ($p < 0.008$ vs 0.01). They also showed improvement in COPD symptoms compared to control group assessed by using CAT score ($p < 0.004$ vs $p < 0.012$), and the Modified Medical Research Council (MMRC) Dyspnoea Scale ($p < 0.002$ vs $p < 0.012$). However, in their study, OPEP has not shown a reduction number of exacerbation in the involved patient. [31, 32]

Improvement in exercise capacity is also proved by a study done by Svenningsen et. al in 2016 in sputum-producer patients. Patients fitted into sputum-producers criteria if they had coughed and brought up sputum “several days a week” (>2 days a week) or “almost every day” in the month prior to the study. Exercise capacity is assessed at baseline, and after Aerobika® OPEP usage at week 3 to 4, and also during final visit at week 6 to 8 using 6MWT. All participants were trained by a pulmonary function technologist to use the device four-times

daily with each session consisting of 10–20 blows into the device, followed by 2–3 "huff" coughs. Treatment sessions were documented at home by the patient using a daily diary. Post OPEP study, in sputum-producers only, it showed significant improvement in 6MWT with *p*-value of 0.04 compared to pre-OPEP group. Their study also proved that the spirometry result (FVC value) in sputum-producer patients with OPEP showed significant improvement compared to off-OPEP group (6% improvement in FVC, $p = 0.02$). [25, 32]

Additionally, Aerobika® OPEP will help to reduce moderate to severe exacerbation. The risk of experiencing subsequent exacerbations is two to four times higher in COPD patients with a prior exacerbation compared to those without prior exacerbation. Therefore, prevention is an important treatment goal [33]. In a study done by Burudpakdee and colleagues in 2017, significantly fewer patients provided with the Aerobika® OPEP device compared to matched controls experienced moderate-to-severe exacerbations (18.5% vs 25.7% respectively, $p = 0.014$) or severe exacerbations (13.8% vs 19.0%, respectively, $p = 0.046$) in 30 days.[34]

There is a study showed that Aerobika® is the most effective OPEP in reducing COPD re-exacerbations compared to other OPEP devices. In a study done by Tse et. al. in 2020 on comparison of impact between two-commonly used OPEP devices; Aerobika® and Acapella® in COPD or chronic bronchitis patients, patients using Aerobika® OPEP had a 31% reduction in COPD or chronic bronchitis related readmission within 30 days of the index hospitalization (12.0% vs. 17.4%; $p = 0.001$) compared to Acapella. This significant difference persisted over a 12-month duration, with a smaller proportion of Aerobika® patients having a severe exacerbation requiring hospitalization (39.6% vs. 45.3%; $p = 0.013$) and fewer hospitalizations per patient (mean, 0.75 vs. 0.90; $p = 0.010$). Aerobika® users also have significantly longer time to first severe exacerbation than Acapella users (log-rank $p = 0.01$). This suggests that Aerobika® OPEP device may be a beneficial add-on to usual care and that OPEP devices may vary in clinical effectiveness. [26]

There is evidence for the cost-effectiveness of the Aerobika® device in the management of COPD, in terms of savings in direct medical costs associated with reduction in COPD exacerbations. By using real-world clinical evidence to evaluate the incremental performance of the Aerobika®, Khoudigian-Sinani et. al. in 2017 analysed data from published literature and national fee schedule to model the cost-effectiveness of Aerobika® OPEP in patients who had experienced an exacerbation in the previous months, or post-exacerbation care population. When the effect of Aerobika® device was assumed to last 30 days, use of the

device resulted in improved outcomes (six fewer exacerbations per 100 patients per year) lead to cost-savings, compared to no OPEP therapy [2]. Similar analysis was done by Thanh and colleagues in 2019 which showed that the Aerobika® OPEP is a potential component of a treatment strategy for symptom control and reduce the risk of re-exacerbations in patients with COPD, with more effective and less costly economic outcome [24]. Therefore, Aerobika® device is a treatment option that provides clinical benefit and results in direct medical cost savings in a post-exacerbation care COPD population in a long run. In real population, usage of OPEP device may be beneficial as it can reduce visits to the emergency department, reduced early rehospitalizations and lower the treatment cost by the means of reducing COPD exacerbation [26, 34, 35].

On the other hand, there is only one study measures the outcome of sputum clearance in COPD patients with OPEP. Svenningsen and colleagues in a study done in 2016 proved that OPEP statistically and clinically significant helpful in improving sputum clearance in sputum-producers COPD patient. Patient Evaluation Questionnaire (PEQ)-ease-bringing-up-sputum score (pre-OPEP 3.9 ± 0.8, post-OPEP 2.7 ± 1.1; $p = 0.005$) is used for evaluation, at which this context, a reduced PEQ score indicates improved sputum clearance [25, 32].

In COPD, sputum clearance might be expected to reduce airflow limitation and allow occluded lung units to be recruited. It is postulated that usage of OPEP can improve small airway disease parameters using IOS. At the moment, there are no studies available on small airway disease parameters improvement after OPEP usage.

In summary, this study would like to propose that non-pharmacological treatment for airway clearance is as important as pharmacological therapy. The aim of the study is to demonstrate that the usage of Aerobika® OPEP device among COPD patients may augment sputum clearance, improve small airway parameters by IOS as well as patient's symptoms as measured by CAT score. In addition, it will also help to improve exercise quality as well as lung function in this group of people.

Figure 2: Oscillating positive expiratory pressure (OPEP) mode of action model [23].

Figure 3: Aerobika® OPEP device

CHAPTER 3

RESEARCH OBJECTIVES

3.1 Objectives

3.1.1 Primary

To demonstrate improvement of small airway parameter using IOS after introduction of Aerobika® OPEP in 3 and 6 months among COPD patients in UKMMC.

3.1.2 Secondary

I. To evaluate improvement of symptoms using CAT score after 3 and 6 months.

II. To evaluate improvement of lung function (using spirometry) and exercise capacity (using 6MWT) after 3 and 6 months.

III. To evaluate moderate and severe exacerbation rates after Aerobika® OPEP device usage in 3 and 6 months.

3.2 Significance of Research

Aerobika® OPEP device is an alternative non-pharmacological therapy to improve patient's symptoms, quality of life, reduce exacerbation and hospitalization, thus will reduce cost of treatment in a long run.

CHAPTER 4

RESEARCH METHODOLOGY

4.1 Type of Study

This is a single center, prospective, interventional study of COPD patients who are under follow up of Respiratory Unit Universiti Kebangsaan Malaysia Medical Center (UKMMC). All patients involved in the study will be given Aerobika® OPEP on top of standard care of COPD.

4.2 Study Design

4.2.1 Period of Study

The study will be conducted from June 2021 to November 2022 after receiving approval by the research ethics committee.

4.2.2 Study Setting

The study will be conducted in the Respiratory Unit, Department of Internal Medicine of Universiti Kebangsaan Malaysia Medical Centre (UKMMC).

4.2.3 Sampling Population

This study will include patients diagnosed with COPD GOLD 2-4 attending the respiratory outpatient clinic UKMMC from June 2021 until November 2022. Demographic and clinical data will be collected. Patient will be followed-up at 3 and 6 months after intervention.

4.2.4 Inclusion Criteria

I. Age 40 years or older
II. COPD diagnosed according to the GOLD guidelines: GOLD 2 - GOLD 4
III. Stable COPD patients with mucus hyperproduction: coughed and brought up sputum “several days a week” (>2 days a week) or “almost every day” in the month prior to the study [25]
IV. Patients who can perform IOS
V. Patients who can perform spirometry

VI. Patients who can perform 6MWT

VII. Patients with small air disease as measured by IOS (R5-R20 > 0.71 $cmH_2O/L/sec$)

4.2.5 Exclusion Criteria

I. COPD diagnosed according to the GOLD guidelines: GOLD 1

II. Diagnosis of other chronic lung diseases: Asthma, Asthma-COPD Overlap, Interstitial Lung Disease, Bronchiectasis, Lung Cancer

III. Patients with contraindication for spirometry: recent cardiac complications, major surgery [36], severe advanced respiratory disease, or those with cognitively or neurologically impairment [37]

IV. Patients not recommended for OPEP: neuromuscular weakness, recent facial, oral or skull surgery or trauma, recent oesophageal surgery, active haemoptysis, acute sinusitis, untreated pneumothorax, known or suspected tympanic membrane rupture or other middle ear pathology, overt right-sided heart failure [23]

V. Patients with contraindication for 6MWT (**Table 1**)

VI. Patient unable or unwilling to give informed consent

VII. Change of inhaler during study period (will be dropped out from study)

Absolute and relative contraindications for field walking tests

Absolute	Relative
Acute myocardial infarction (3–5 days)	Left main coronary stenosis or its equivalent
Unstable angina	Moderate stenotic valvular heart disease
Uncontrolled arrhythmias causing symptoms or hemodynamic compromise	Severe untreated arterial hypertension at rest (200 mmHg systolic, 120 mmHg diastolic)
Syncope	Tachyarrhythmias or bradyarrhythmias
Active endocarditis	High-degree atrioventricular block
Acute myocarditis or pericarditis	Hypertrophic cardiomyopathy
Symptomatic severe aortic stenosis	Significant pulmonary hypertension
Uncontrolled heart failure	Advanced or complicated pregnancy
Acute pulmonary embolus or pulmonary infarction	Electrolyte abnormalities
Thrombosis of lower extremities	Orthopedic impairment that prevents walking
Suspected dissecting aneurysm	
Uncontrolled asthma	
Pulmonary oedema	
Room air S_{pO_2} at rest ≤85%#	
Acute respiratory failure	
Acute noncardiopulmonary disorder that may affect exercise performance or be aggravated by exercise (*i.e.* infection, renal failure, thyrotoxicosis)	
Mental impairment leading to inability to cooperate	

Table 1: Absolute and relative contraindications for field walking tests [38]

4.3 Study Protocol and Data Acquisition

This is a prospective interventional study conducted on COPD patients (GOLD 2-4) under the Respiratory Unit, Department of Internal Medicine in UKMMC, who qualified both the inclusion and exclusion criteria. Beforehand, all potential subjects will undergo screening and survey to exclude any possible symptoms of COVID-19 disease. All eligible patients will be briefed about this study.

Subsequently, consent will be obtained from those who are agree to participate, either from the patient him/herself or their next-of-kin. The process of briefing and obtaining consent will be only done once the patient is stable. These processes will not in any way interfering with clinical evaluation, investigation, treatment and intervention done to the patient by the attending doctor. All of the consented patients will be given Aerobika® OPEP.

Prior to the initiation of Aerobika® OPEP device, baseline of IOS parameters, symptoms (using CAT score), lung function (using spirometry-FEV_1 and FVC), exercise capacity (using 6MWT) and exacerbation episodes of the past 6 months will be done and recorded in data collection sheet. All recruited patients will receive OPEP and trained to use for 10 minutes, 2 times per day [32]. Patients also will be emphasized that standard care for COPD management will be continued. An adherence sheet will also be provided to patients at which they can put crosses when they use the device as advised. They are encouraged to use Aerobika® immediately after using their inhalers in order to increase adherence of treatment.

Patients will be given phone call 2 days after they received Aerobika® as a reminder and also to ensure they are using it in a correct way. At week 12 and week 24 of Aerobika® OPEP usage, their IOS parameters, symptoms (using CAT score), lung function (using spirometry-FEV_1 and FVC), exercise capacity (using 6MWT) and exacerbation episodes will be reassessed. During clinic visit also, his/her standard management for COPD will be checked to ensure no change in the inhaler regime. Within the study period of 6 months, patient will be given follow-up phone calls every two to three weeks to ensure their adherence toward Aerobika®.

The entire clinical information will be retrieved from the medical department clerking chart and electronic health care record system of the studied patients. The follow-up data will be retrieved from the digital and written patient records to identify the frequency of exacerbation and any hospitalization. In cases where follow-up data are incomplete or missing, the patient or his/her next-of-kin will be called to obtain information on their condition, hospital admission, clinical and functional status.

4.4 Operational Terms Definition

4.4.1 Chronic Obstructive Pulmonary Disease (COPD)

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases [(3)]

4.4.2 COPD Exacerbation

COPD exacerbation is defined as:

I. Mild COPD exacerbation was defined as worsening of symptoms that were self-managed (by measures such as an increase in salbutamol use) and resolved without systemic corticosteroids or antibiotics
II. Moderate exacerbation if treated with systemic steroids and/or antibiotics
III. A severe exacerbation if hospitalisation is required for treatment of exacerbation or admission to emergency > 24 hours [(39)]

4.4.3 COPD Staging based on GOLD

GOLD STAGE	SEVERITY	FEV_1
Stage 1	Mild	$FEV_1 > 80\%$ predicted
Stage 2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
Stage 3	Severe	$30\% \leq FEV_1 < 50\%$ predicted
Stage 4	Very severe	$FEV_1 < 30\%$ predicted.

Table 2: Classification of Airflow Limitation Severity (Based on Post-Bronchodilator FEV_1)[(3)]

4.5 Sample Size

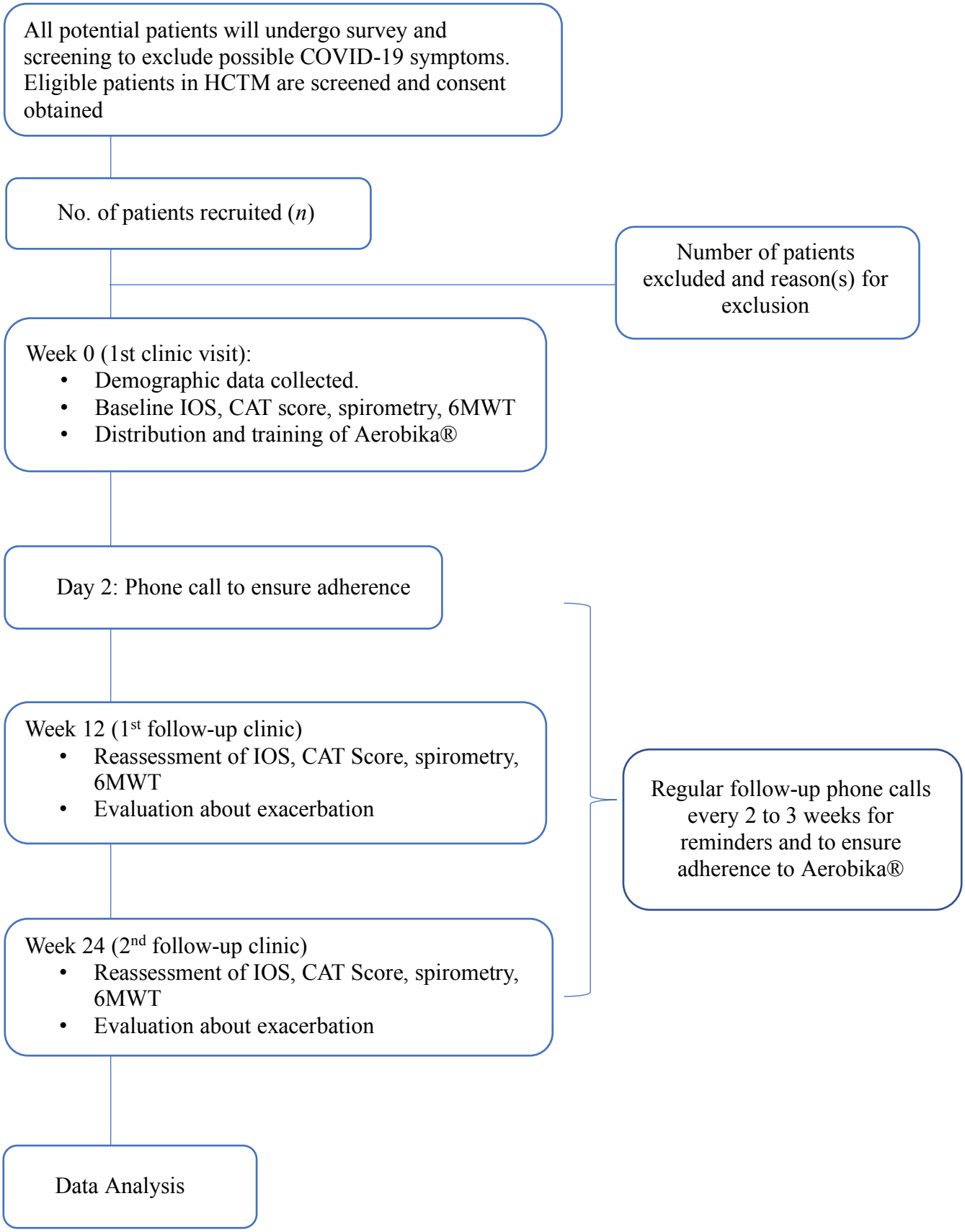
According to Cohen's d formula, Cohen suggested that effect size of 0.2, 0.5 and 0.8 as small, medium and large effect size respectively. Effect sizes are the most important outcome at which the researchers want to know whether an intervention or experimental manipulation has an effect greater than zero, or (when it is obvious an effect exists) how big the effect is [40]. In our study, we aim to have a medium effect size with the usage of Aerobika®. An effect size of 0.5 is described as medium and is 'large enough to be visible to the naked eye' [41].

By using online statistical calculator apps; Sample Size Calculator for Comparing Paired Differences, this study would require a sample size of 34 to achieve a power of 80% and a level of significance of 5% for detecting an effect size of 0.5 paired differences (Dhand, N. K., & Khatkar, M. S. (2014). Statulator: An online statistical calculator. Sample Size Calculator for Comparing Two Paired Means. http://statulator.com/SampleSize/ss2PM.html.

Additional of 40% samples is recruited to avoid subject consent withdrawal, drop out, or missing data. Therefore, a total of minimum 48 patients will be recruited for this study. However, we aim to recruit 60 patients as we were sponsored 60 units of Aerobika® OPEP.

The outcomes of this study will be evaluated on all patients by comparing all the parameters during baseline and at 3- and 6-months follow-up after using Aerobika®. There will be no non-interventional arm as the sample size will become bigger. During the COVID-19 pandemic era, we would like to reduce the exposure towards those performing respiratory tests. The other limitations as well with larger sample size are budget and time constraint.

4.6 Data Collection Pathway



4.7 Dummy Table

Table 1: Baseline demographic date

Variables	Study population (n= _)	Stage 2	Stage 3	Stage 4	*p*-value
Age (mean +/- SD)					
Gender Male Female					
Ethnicity Malay Chinese Indian Others					
BMI (kg/m2)					
COPD Duration					
Education Primary Secondary Tertiary					
Smoking status Yes No					
Comorbidities					

Table 2: IOS, CAT score, Spirometry, 6MWT and Exacerbation at Week 0, 12 and 24 for each COPD stage

COPD stages:	Stage 2			Stage 3			Stage 4		
Week:	0	12	24	0	12	24	0	12	24
CAT Score									
6MWT									
Exacerbation									
FEV_1 (L predicted) FEV_1 (%predicted) FEV_1/FVC (%) FEF 25-75 (L predicted) FEF 25-75 (% predicted) R20 ($cm/H_2O/L/sec$) R5 ($cm/H_2O/L/sec$) R5-R20 ($cm/H_2O/L/sec$)									

CHAPTER 5

RESEARCH ETHICS

Approval from the Research and Ethics Committee of Universiti Kebangsaan Malaysia Medical Centre (UKMMC) will be sought in order to commence the study. All the collected information will be strictly confidential and only accessible by the research team members. All patients will be kept anonymous and coded into the data collection sheet.

Participants will only be recruited in this study if informed consent was given, and will be allowed to withdraw from the study at any point. The research will be conducted according to standard of good clinical practice and the rights and safety of the participants are guaranteed throughout the study.

CHAPTER 6

FINANCIAL PLANS

Items	Justification	Quantity	Total (RM)
VOTE 27000: Research Items			
Microguard Bacterial Filter	Single use for every patient's test	RM 19.50 x 180 pcs	RM 3 510.00
Disposable Mouthpieces	Single use for every patient's test	RM 4.50 x 180 pcs	RM 810.00
Calibration Gas	Gas is used for operational standard for IOS and spirometry.	RM 4.50 x 180 pcs	RM 3 200.00
		Total	**RM 7 520.00**
VOTE 29000: Professional Service (Perkhidmatan Ikhtisas)			
Honorarium for Respiratory Laboratory Technicians	Incentives for the involved respiratory unit technician who have expertise in handling the machines	RM 15 x 180 patients	RM 2 700.00
		Total	**RM 2 700.00**
		GRAND TOTAL	**RM 10 220.00**

CHAPTER 7

RESEARCH INFORMATION

INFORMATION SHEET

(In reference for next-of-kin)

Research Title:

Impact of Aerobika® Oscillating Positive Expiratory Pressure (OPEP) in Improving Small Airway Disease and COPD Assessment Test (CAT) Score in Chronic Obstructive Pulmonary Disease (COPD)

Researcher's Name:

Associate Professor Dr Mohamed Faisal Abdul Hamid / Dr Siti Nurhanis binti Sahardin

Place of Conduct:

Respiratory Unit, Department of Internal Medicine, Universiti Kebangsaan Malaysia Medical Centre (UKMMC).

Introduction:

COPD is a progressive airway disease, at which patients will have mucus hypersecretion and progressive severity of airflow limitation that cause difficulty in breathing and reduce in quality of life. This disease is also characterized by a mixture of small airway disease and parenchymal

lung tissue destruction causing emphysema which affecting gas transfer. Prevalence of small airway disease in COPD is higher with more advanced COPD stages.

Aerobika® OPEP is a device to help for improvement in small airway disease in COPD patients measured by impulse oscillometry (IOS). IOS is a simple test at which patient has to breath normally through a device without any extra effort. It can also help with symptoms and sputum clearance as well. On the other hand, Aerobika® can improve patient's lung function test, exercise capacity, and at the same time help to reduce exacerbation rate which in long run can reduce hospitalization and treatment cost. With the use of Aerobika® OPEP device, patient can actively take part in the management of COPD at home. This device can be used on a daily basis in the comfort of your home, without any additional risk.

Purpose of Study:

This study aims to demonstrate that the usage of Aerobika® OPEP can help to improve small airway diseases and symptoms in COPD (GOLD 2-4) patients. Other than that, it can help to improve quality of life as well as reduce exacerbation rate of COPD.

Type of Intervention:

On top of your current standard care for COPD, you will be given Aerobika® OPEP device once consented for this study. During first visit, we will assess your symptoms and small airway disease parameters, as well as lung function test, 6 Minutes Walking Test (6MWT) and exacerbation episodes. Subsequently, we will see you in clinic after 12 and 24 weeks for follow up to reassess back all the parameters to compare for any improvement after Aerobika® OPEP usage.

Benefits of joining in this study:

- You can know your degree of small airway disease parameters, exercise capacity as well as severity of airway limitation and it will be monitored closely.
- Your medications will be reviewed accordingly to ensure effective standard care of treatment
- Your symptoms will be monitored by a standard clinical questionnaire.
- You will be monitored closely by the same doctor throughout the study.

Risk of joining in this study:

- There is no risk or added cost for using Aerobika® or IOS.

Participation in this study is entirely voluntary. It is your choice to participate (or allow patient to participate). Regardless of your choice, the standard quality of care and treatment remain the same. All data obtained will be recorded and will be used for analysis.

Confidentiality:

Information collected during this study will be kept confidential. Access to the data is only by the researcher team and the Research Ethics Committee of UKMMC. No specific reference to any individual will be reported in this study. Participants have the right to know the outcome of this study.

Reimbursements:

Participants do not have to pay for the lung function test, nor be paid for participating in this study.

Right to Refuse or Withdraw:

This study is of voluntary basis, patient or his/her next-of-kin have the right to withdraw from this study at any time of the study. The choice is yours and all your right will be respected.

Who to contact:

1) Dr Siti Nurhanis binti Sahardin (+60133086481).
   Respiratory Unit, Department of Internal Medicine, University Kebangsaan Malaysia Medical Centre, UKMMC.

2) Associate Professor Dr Mohamed Faisal Abdul Hamid (+60391456108).
   Respiratory Unit, Department of Internal Medicine, University Kebangsaan Malaysia Medical Centre, UKMMC.

Figure: Aerobika® OPEP

CHAPTER 8

INFORMED CONSENT FORM

Research Title:

Impact of Aerobika® Oscillating Positive Expiratory Pressure (OPEP) in Improving Small Airway Disease and COPD Assessment Test (CAT) Score in Chronic Obstructive Pulmonary Disease (COPD)

Researcher's Name:

Associate Professor Dr Mohamed Faisal Abdul Hamid / Dr Siti Nurhanis binti Sahardin

I, ……, IC No: …..…….....,

- Have read all the information in the Patient Information Sheet and understand the aim and purpose of this study.
- Have been given enough time to think about it and all of my question have been answered to my satisfaction.
- Understand that I may freely choose to withdraw from this study at any time without reason and without repercussions.
- Understand that anonymity will be ensured in the final write up.

I understand all the above and voluntarily agree to take part in this research study, to follow the study procedures and to provide the necessary information as requested.

……..……	……....…….
Signature/Thumbprint	Date
……..……..	……...……
Witness Signature	Researcher Signature
……...	Siti Nurhanis binti Sahardin (880504-01-5504)
Witness Name /IC no	Researcher Name/ IC no
……...	……
Date	Date

CHAPTER 9

DATA COLLECTION SHEET

PATIENT'S STICKER

Name. : ……..…

Contact Number: …….…….

Age : ……..

Gender : …….……

Ethnicity : …….…….

Background Medical Problem:

- Diabetes Mellitus ☐
- Hypertension ☐
- Ischaemic heart Disease ☐
- Heart Failure ☐
- Previous stroke ☐
- Dyslipidaemia ☐
- Others:

  ……

  …….

Weight: ……. Height: ……. BMI: ……

First diagnosis of COPD: ……. MMRC Class: ……. COPD stage: ……

Number of exacerbations in the past 6 months : ……..…….……

Current COPD inhalers: ……..……...

Inhaler technique: ……

Week:	0	12	24
CAT Score			
6MWT			
Exacerbation			
FEV_1 (L predicted) FEV_1 (%predicted) FEV_1/FVC (%) FEF 25-75 (L predicted) FEF 25-75 (% predicted) R20 (cm/H_2O/L/sec) R5 (cm/H_2O/L/sec) R5-R20 (cm/H_2O/L/sec)			

CHAPTER 10

GANTT CHART

	November 2020- January 2021	January 2021	January 2021- June 2021	June 2021- November 2022	November 2022- January 2023	January 2023-April 2023	April 2023-May 2023
Literature review							
Proposal correction, submission and presentation							
Ethics Committee Approval							
Recruitment of study subjects							
Data entry and analysis							
Writing report and thesis submission							
Thesis presentation							

CHAPTER 11

APPENDICES

Appendix A:

Modified Medical Research Council (MMRC) Questionnaire for Categorizing COPD Severity.

Severity	Score	Level of Breathlessness
None	0	Only breathlessness with strenuous exercise
Mild	1	Shortness of breath hurrying or walking up a slight hill
Moderate	2	Walks slower than age group or has to stop for breath when walking on level ground at own pace
Severe	3	Stops for breath after walking 100 meters or a few minutes on level ground
Very severe	4	Breathless when dressing/undressing or too breathless to leave the house

Appendix B:

UKMMC Medical COVID-19 Assessment Form

UNIVERSITI KEBANGSAAN MALAYSIA
The National University of Malaysia

HOSPITAL CANSELOR TUANKU MUHRIZ

MEDICAL COVID-19 ASSESSMENT FORM

DATE: _____

Particular Patient:

NAME: _____
IC NUMBER: _____
ADDRESS: _____
CONTACT NUM: _____

CONTENT	YES	NO
RISK EXPOSURE		
1.Travel to or residence in known high risk area within the last 14 days		
2.Close contact with a pneumonia case of unknown cause linked to COVID 19 cluster within 14 days before onset of illness		
3.Contact with COVID patients/PUI/Quarantine individual/ Tabligh/any high risk cluster		
CLINICAL SIGN AND SYMPTOMS		
1.Fever (>38 C)		
2.Sore throat		
3.Cough (mostly dry)		
4.Difficulty of breathing		

Assessed by: _____

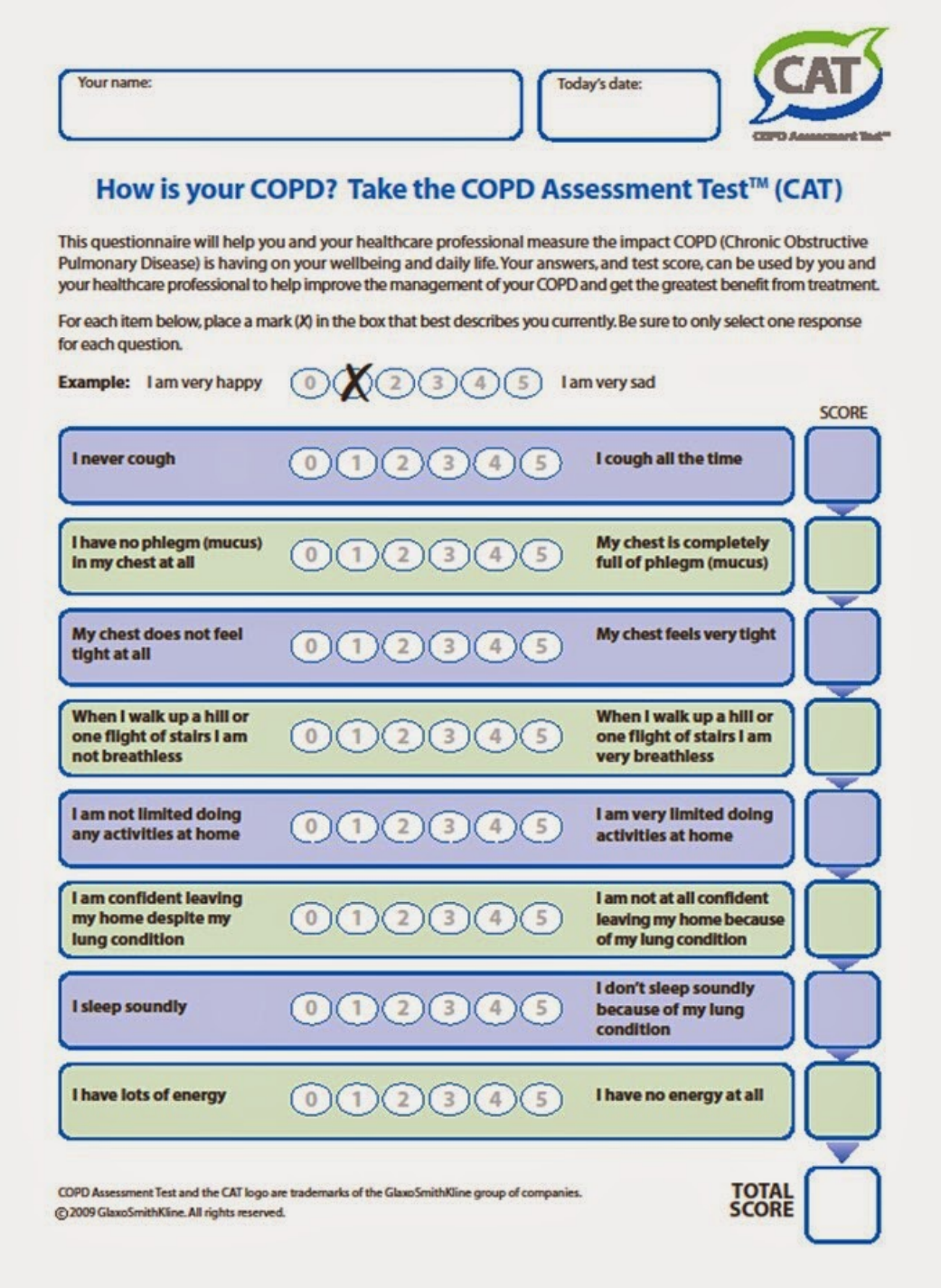
Signature: _____

MS ISO 9001:2015 Cert No.: QMS 01547

JABATAN PERUBATAN
Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia
Tingkat 6 , WAD 6E , Bangunan Klinikal, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur.
Telefon: +603-9145 7603/7604/7673 | E-mel: wad6e@ppuk.ukm.edu.my
Laman Web: http://www.ppukm.ukm.my

Appendix C:

COPD Assessment Test (CAT) Score



Your name:

Today's date:

CAT

COPD Assessment Test™

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	

TOTAL SCORE

COPD Assessment Test and the CAT logo are trademarks of the GlaxoSmithKline group of companies.
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The CAT is available and free to use globally (no charges will be associated with its use) in the situations described in the terms of use on the CAT website [42].

Appendix D:

6 Minutes Walking Test (6MWT)

UNIT RESPIRATORI
MAKMAL PEMERIKSAAN KLINIKAL
JABATAN PERUBATAN
PUSAT PERUBATAN UKM
03-91455555 ext: 5581/6108

6 MINUTES WALKING TEST REPORT

A. DEMOGRAPHIC DATA

Patient name : _____ Age : _____ years old
Patient ID : _____ Height: _____ cm
Gender : M ☐ F ☐ Weight: _____ kg

B. BORG SCALE

Parameter	Description
0	Nothing at all
0.5	Extremely weak
1	Very weak
2	Weak (light)
3	Moderate
4	Somewhat Strong
5	Strong (Heavy)
6	
7	Very Strong
8	
9	
10	Extremely Strong
*	Maximal

C.TEST

Parameter	Start of test	End of test
Fatique (Borg scale)		
Dyspnea (Borg scale)		
SPO2 (%)		
Pulse rate (%)		
Blood Pressure		

D. RESULT

Stopped or paused before 6 minutes? No ☐ Yes ☐ , reason: _____
Number of laps: _____ (6 meters)
Total distance walked in 6 minutes: _____ meters

E. TECHNICIAN COMMENT

_____

Name : _____

Sign : _____

Date : _____

Appendix E:

Adherence Sheet

Name/Nama: ……. MRN: ……

Year/Tahun: …….. Month/Bulan: ……

Please put cross (X) if you have used your Aerobika® for 10 minutes

Sila tandakan pangkah (X) bila anda sudah menggunakan Aerobika® selama 10 minit

Date	8am	4pm
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		

Date	8am	4pm
17		
18		
19		
20		
21		
22		
23		
24		
25		
26		
27		
28		
29		
30		
31		

CHAPTER 12

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