UNIVERSITI KEBANGSAAN MALAYSIA
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DEPARTMENT OF INTERNAL MEDICINE
UNIVERSITI KEBANGSAAN MALAYSIA

Official Title : A Randomised, Open Label, Interventional Study Evaluating the Efficacy & Safety of Dry Powder Ivy Extract (Syrup Prospan) versus NAC among COPD Patients

(SyProNAC Trial)

Research Identification Number : FF-2023-433
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Section 1: Introduction

As the third global leading cause of death, Chronic Obstructive Pulmonary Disease (COPD) affects more than 300 million people worldwide [1,2]. These patients suffer from 0.5–3.5 exacerbations per year on average. Each exacerbations dampened their health status as well as quality of life, not to mention a great burden to our healthcare system [3,4]. Those partially treated or prolonged exacerbations would subsequently lead to unfavorable disease progression. Hence a holistic approach in managing each exacerbations is very crucial [5].

Mucus hypersecretion in COPD patients plays a pivotal role in acute exacerbations and associated with unfavorable outcomes [6]. These exacerbations comes with sputum increment as much as its purulence. Mucolytics are believed to to ease patient to expectorate and benefits them from tip into an exacerbations or even the consequent hospitalisation [7].

Mucolytics work by reducing sputum viscosity hence improved its expectoration. N-acetylcysteine (NAC) is a mucolytic with antioxidant and anti-inflammatory properties, commonly used in practice among COPD patients [8]. Meanwhile, Syrup Prospan is ivy leaf preparations, obtained as extracts from leaves of the plant Hedera helix L. It is widely used over-the-counter cough remedy containing saponins which are believed to have expectorant properties [9]. Studies show evidence of antispasmodic, bonchodilating, anti-inflammatory and antitussive properties and its usage is authorised by the European Medicines Agency [10].

Section 2: Literature Review

Mucolytics are defined as medications that decrease mucus viscosity and can be divided into classic and peptide mucolytics. Classic and peptide mucolytics depolymerize mucin glycoproteins and DNA with F-actin polymer networks, respectively [11].

NAC alters mucus viscosity by modifying the crosslinks and molecular interactions within mucin polymers. These changes enhancing mucociliary clearance and subsequent sputum expectoration. This effects are beneficial in mucus hypersecretory states such as COPD and cystic fibrosis.

Several studies on NAC suggest apart from its mucolytic properties, it exerts anti-inflammatory effects by inhibiting chemotaxis, reducing lysozymes and lactoferrin concentration as well as neutrophils and macrophages in bronchoalveolar lavage fluid [12]. In addition, it inhibits bacterial adherence to the ciliated epithelium [13].

Latest 2023 GOLD Report stated that COPD patients not receiving ICS, regular treatment with mucolytics such as carbocysteine and N-acetylcysteine (NAC) may reduce exacerbations and modestly improve health status.

A meta-analysis by Papadopoulou et al included 24 RCTs involving 2192 patients with COPD exacerbations demonstrated with moderate certainty that mucolytics appear to improve the treatment success rate and symptoms [14].

Another meta analysis conducted by Cazzola et al demonstrates that mucolytics are useful in preventing COPD exacerbations as maintenance add-on therapy to patients with frequent exacerbations. The effectiveness of mucolytics is independent of

the severity of airway obstruction and the use of inhaled corticosteroids [15].

Various trials proved the efficacy and safety of ivy leaves preparation for acute URTI and also chronic bronchitis. Schaefer et al proved consistent superiority of ivy leaves cough liquid in a randomized, placebo-controlled, double-blind trial [16]. A cohort study in Germany provided further evidence that the use of ivy leaves preparations contribute to inappropriate antibiotic usage for respiratory infections in adult patients with cough symptoms [17].

To date there are no studies comparing Ivy leaf preparations with other mucolytic agents. A meta analysis by Rogliani et al assessed the efficacy of erdosteine, carbocysteine, and NAC on acute exacerbation and concluded that overall efficacy and safety profile of erdosteine is superior to that of both carbocysteine and NAC [18].

Section 3: Hypothesis

1. Syrup Prospan is non inferior to NAC - no significant difference of cough symptoms and its impact on daily activities, health related quality of life, as well as lung function test at 30 days of treatment
2. Patients received Syrup Prospan has higher satisfaction score compared to N-Acetylcysteine

Section 4: Research Objectives

Primary objective

To demonstrate that Syrup Prospan is non inferior to N-Acetylcysteine in assessment of cough symptoms and its impact on daily activities using Cough and Sputum Assessment Questionnaire (CASA-Q) during 30 days of treatment.

Secondary objective

1. To evaluate the effectiveness of Syrup Prospan vs N.Acetylcysteine in terms of

   I. McGill COPD Quality of Life Questionnaire on Day 1 and 30 days of treatment.
   II. Lung function test (including morning pre-dose FEV1) and FVC on Day 1 and 30 days of treatment.
   III. Incidence of adverse effects (in %)

2. To assess satisfaction of treatment using the 5 point Likert Scale.

Section 5: Research Design & Methodology

5.1 Study Design

A randomised, open label, interventional study evaluating the efficacy and safety of dry powder Ivy Extract (Syrup Prospan) versus NAC among COPD patients.

Randomization 1:1 to received either N.Acetylcysteine 600 mg BD or Syrup Prospan 7.5mls BD (Block randomization)

5.1.1 Period of Study

The study will be conducted from December 2023 to November 2026 after receiving approval by the research ethics committee.

5.2 Sampling Population

This study will include All patients are stable COPD patients under Respiratory Clinic HCTM follow-up, aged ≥ 40 year old and above and able to perform spirometry from September 2023 to February 2024. Demographic and clinical data will be collected. Patient will be followed-up at Day 15 and Day 30 after intervention.

5.3 Inclusion and Exclusion Criteria

Inclusion criteria

1. Patients with documented post bronchodilator FEV1/FVC < 70 or <LLN
2. Age 40 years and above
3. Able to perform spirometry
4. Patient with Stable COPD based on GOLD 2023 strategy

Exclusion criteria

1. Diagnosis of other chronic lung diseases: Asthma, Asthma-COPD Overlap, Interstitial Lung Disease, Bronchiectasis, Lung Cancer
2. Patients with contraindication for spirometry: recent cardiac complications, major surgery, severe advanced respiratory disease, or those with cognitively or neurologically impairment
3. Hypersensitivity to acetylcysteine or any component of the formulation
4. Hypersensitivity to dry powder ivy extract
5. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG (human Chorionic Gonadotropin) laboratory test
6. Patients on pre-existing regular mucolytics (at least 1 month prior)
7. Illiterate patients

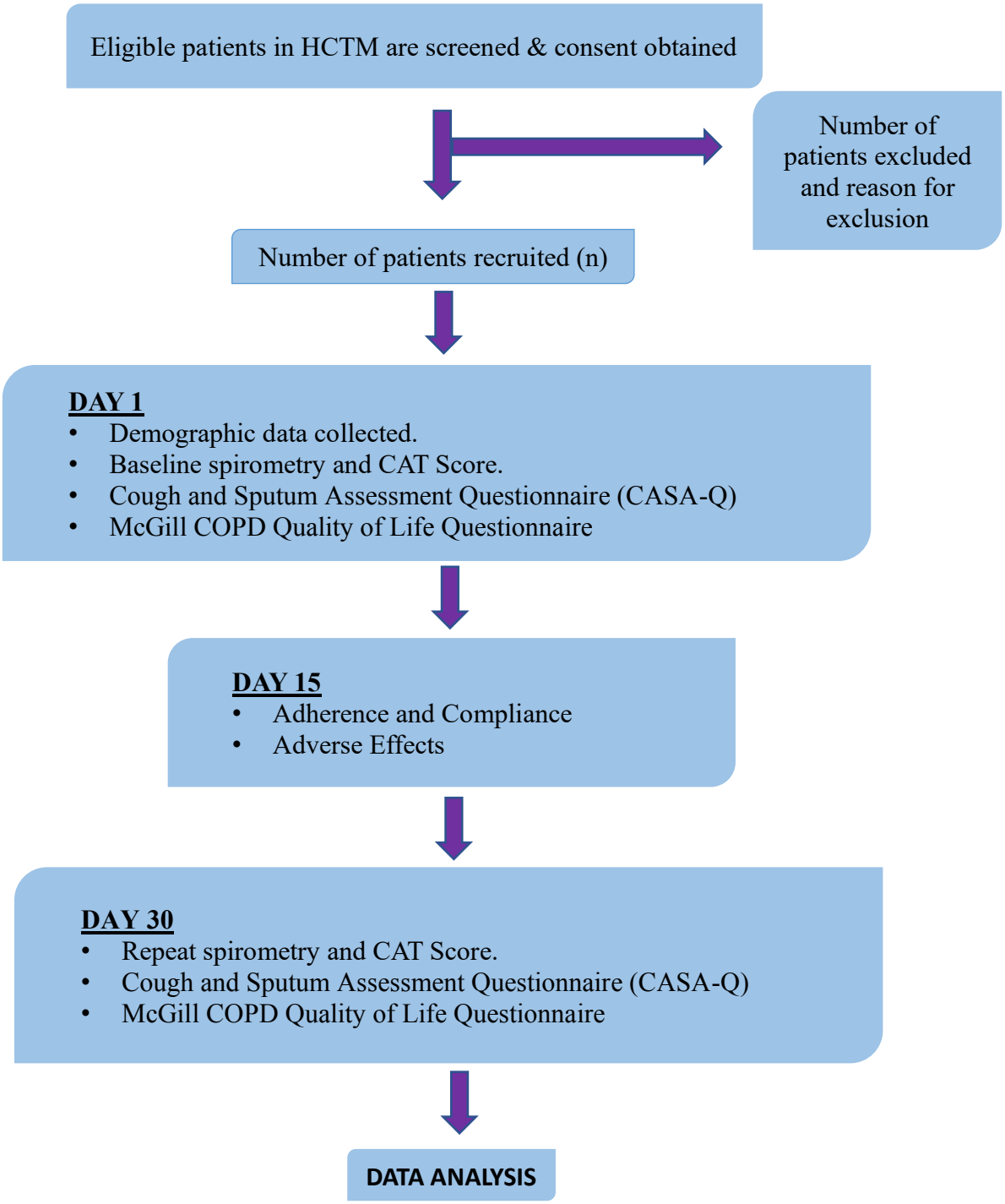
5.4 Study Protocol and Data Acquisitions

This is a prospective interventional study conducted on COPD patients under the Respiratory Unit, Department of Internal Medicine in HCTM, who qualified both the inclusion and exclusion criteria. Patients will be briefed about this study.

Subsequently, consent will be obtained from those who are agree to participate from the patient him/herself.

Patients' will be assessed first with several modalities particularly spirometry, CAT score, McGill COPD Quality of Life and Cough and Sputum Assessment Questionnaire (CASA-Q) prior to the commencement of treatment. Patients will be seen on Day 15 to evaluate patients' adherence, compliance as well as adverse effect. Then patients will be assessed again on Day 30 of treatment with the same set of evaluation tools as in the beginning of the study.

5.4.1 Recruitment/Data Collection Pathway



5.5 Operational Term Definitions

Stable COPD based on GOLD 2023 strategy

All outpatient COPD patients, GOLD I, II, III, IV as per GOLD 2023 Guidelines seen in Respiratory Clinic HCTM and not in exacerbation upon recruitment

Exacerbation (as per GOLD Executive Summary)

An event in the natural course of the disease characterise by change in the patient's baseline dyspnoea, cough and/or sputum beyond normal day-to-day variation that is acute onset and may warrant change in regular medications

Adherence and compliance

Using pill count method, the adherence rate is determined by the following formula

% adherence = (Quantity dispensed) - (Quantity remaining) / (Prescribed no of tablets/day) x (No of days between dispensing date and interview)

For Syrup Prospan we will quantify by determine the volume of syrup

Adverse Effects

Any desirable effects that experienced by patients after started on the aforementioned medication

5.6 Sample Size and Power of Study

In order to calculate the required sample size, we will employ the Cohen's d formula for estimating the effect size (Cohen, 1988) [19]. The formula is given as

$$d = \frac{M_1 - M_2}{\sqrt[2]{\frac{SD_1^2 + SD_2^2}{2}}}$$

Where d is the Cohen's effect size, M_1 and M_2 are the mean for the first and second group, and SD_1 and SD_2 are the standard deviation for the first and second group respectively.
Based on a similar study by Kuzmenko et al. (2020) [20] which employs the CAT score to assess the efficacy of NAC in patients with COPD, the mean and standard deviation for before and after treatment are given as:

Before treatment: 23.46 ± 3.66
After treatment: 20.38 ± 5.78

Hence, this give the values of $M_1 = 23.46$ and $M_2 = 20.38$, and $SD_1 = 3.66$ and $SD_2 = 5.78$ that can use to estimate the effect size using the formula above.

$$d = \frac{23.46 - 20.38}{\sqrt[2]{\frac{3.66^2 + 5.78^2}{2}}} = 0.637$$

Therefore, it gives an estimated effect size of 0.637 which is considered to be a medium effect size.

With a power of 80% and a level of significance of 5% for detecting an effect size of 0.637, we calculate the required

sample size using an online sample size calculator (Dhand & Khatkar, 2014) [21] for comparing paired differences. It gives at a value of 23 participants for each group which mean the required number of participants is 46.

Additional of 20% samples is recruited to avoid missing data due to withdrawal or drop out. Therefore, a total of minimum 55 patients will be recruited for this study. However, we aim to recruit 100 patients for our study where the treatment is given to equal number of participants in each group.

Section 6: Statistical Analysis

Data were collected manually with a data collection sheet. Demographic data and patient characteristic will be analysed using descriptive analysis and Chi-square method. Continuous variables were presented as mean ± SD and categorical variables as percentages, unless stated otherwise.

All statistical analysis for the study will be performed using statistic software SPSS version 24.0 (IBMSPSS Statistics 2017). A p-value of <0.05 is considered statistically significant.

Section 7: Research Ethics

Approval from the Research and Ethics Committee of Hospital Canselor Tuanku Muhriz onbtained with research code FF-2023-433. . 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.

Participant 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.

Section 8: Estimated Cost of Study

ACTIVITY / DEVICE	AMOUNT	COST PER ITEM	ESTIMATED COST
Syr Prospan 7.5ml BD (Sponsored by DELFI)	450ml (4 and half bottle) x 50 patients	RM18.9 per bottle	RM4725
Tab NAC 600mg BD (Sponsored by DELFI)	60 tablets x 50 patients	RM3.29 per tablet	RM9870
Printing:			
i) Research Information	2 pages for each set x 100	RM0.40	RM48
ii) Consent form	1 page for each set x 100	RM0.20	RM24
iii) Data collection sheet	2 pages for each set x 100	RM0.40	RM48
iv) CAT Score Questionnaire	1 page for each set x 100	RM0.20	RM24
v) McGill COPD QoL Questionnaire	6 pages for each set x 100	RM1.20	RM144
TOTAL ESTIMATED COST			RM14883

Section 9: Research Information Sheet

Research Title:

A Randomised, Open Label, Interventional Study Evaluating the Efficacy & Safety of Dry Powder Ivy Extract (Syrup Prospan) versus NAC among COPD Patients

Researcher's Name:

Dr Mas Fazlin Mohamad Jailaini / Dr Muhamad Thaqif bin Sidek

Place of Conduct:

Respiratory Unit, Department of Internal Medicine, Hospital Canselor Tuanku Muhriz

Introduction:

COPD is a progressive airway disease and mucolytics help controlling symptoms as well as prevent future exacerbations.NAC is a common mucolytic agent and Syrup Prospan is ivy leaf preparations used to serve this purpose.

***Purpose of Study*:**

This study aims to evaluating the efficacy and safety of Ivy Extract preparations against NAC as mucolytic in COPD patients.

***Type of Intervention*:**

You will be randomised either in 'Interventional group' or 'non-interventional group'. For the interventional group, we will change your mucolytic agent to Syrup Prospan. For the non-interventional group, we will continue your current NAC. We will first get a baseline spirometry, CAT score, McGill COPD QoL Questionnaire and CASA-Q on D1. We will continue follow-up closely for both group and assess your adherence to medications and adverse effects on D15 and finally on D30 of treatment with repeat spirometry, CAT score, McGill COPD QoL Questionnaire and CASA-Q.

Risk of joining in this study:

- There are no surgical intervention / life threatening side effects involved with this study, therefore no major risk is associated upon enlistment.
- The documented side effects for both medications are as follows;
    - NAC – anaphylaxis; skin rash, urticaria, bronchospasm, angioedema
    - Ivy Leaf Extract – nausea, vomiting, diarrhoea, allergic reaction

    *If you experiences any side effects other than mentioned above, kindly inform us for subsequent appropriate measures.

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 HCTM. 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 spirometry, 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.

Section 10: Consent Form

Research Title:
A Randomised, Open Label, Interventional Study Evaluating the Efficacy & Safety of Dry Powder Ivy Extract (Syrup Prospan) versus NAC among COPD Patients

Researcher's Name:

Dr Mas Fazlin Mohamad Jailaini / Dr Muhamad Thaqif bin Sidek

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 Name/IC no:
DATE:

…….
Researcher Name/IC no: Dr Muhamad Thaqif Sidek (900617-10-6037)
DATE:

Section 11: Data Collection Sheet

Patient's Sticker

Contact Number: ……...

Age: …….

Gender: ……...

Ethnicity: ……

<u>Background Medical Problem:</u>

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

Weight: …….
Height: ……..
BMI: …….

First diagnosis of COPD: ……
MMRC: ……
CAT Score:……...

Number of exacerbations in the past 1 year: …….

Date of recent spirometry: …….

FEV1 (post-bronchodilator): …….

<u>Types of inhalers:</u>

<u>Inhaler technique:</u>
Correct ☐ **Incorrect** ☐

	D1	D30
Spirometry		
CAT score		
McGill COPD QoL		
CASA-Q		

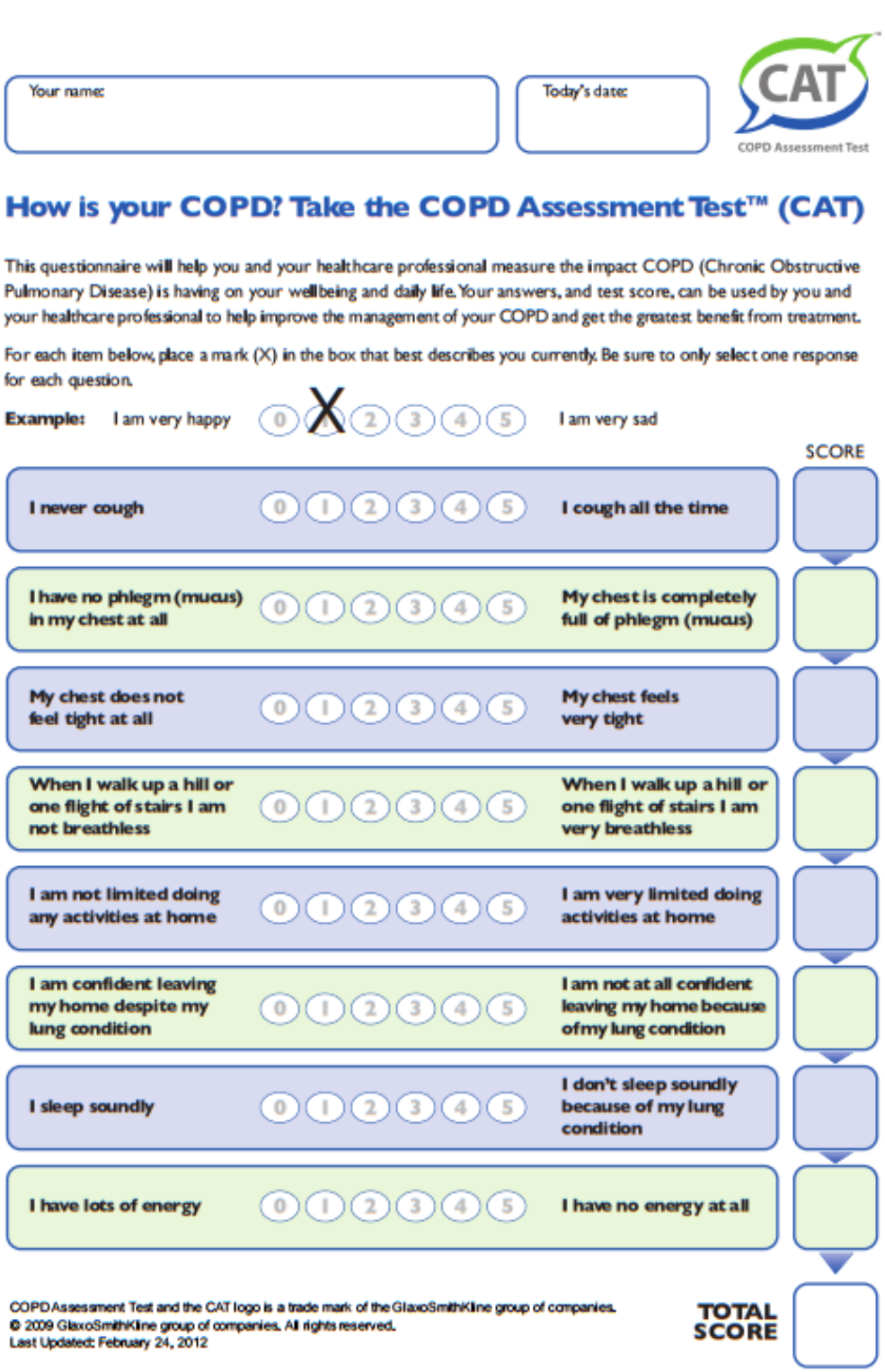
Adherence: …….
.

Adverse effects: ……...

Section 12: Gantt Chart

Progression / Timeline	Mac 2023 - May 2023	Jun 2023 - Oct 2023	Dec 2023	Jan 2024 - Dec 2024	Dec 2024 - Dec 2025	Jan 2026 - Oct 2026	Nov 2026
Literature review							
Proposal preparation, correction and presentation to Medical Department, UKMMC							
Approval of UKMMC Research and Ethics Committee							
Patient recruitment							
Data entry and analysis							
Final result and manuscript submission							
Thesis presentation							

Section 13: Appendices



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

Last Updated: February 24, 2012

HRN Pulmonary Rehabilitation Research Infrastructure
COPD Research Axis

McGill COPD Quality of Life Questionnaire

Centre |_|_|_| Project |_|_|_| Subject Visit |_|_|_| |_|_|_| |_|

Pre-rehabilitation evaluation (visit 1) ☐ Post-rehabilitation evaluation < 1 month (visit 2) ☐

Post-rehabilitation evaluation : 1 yr (visit 3) ☐ 2 yrs (visit 4) ☐ 3 yrs (visit 5) ☐

Date |_____|_____|_____| yyyy-mmm-dd Time at the beginning of the questionnaire |_____:_____| on 24:00

Current or recent exacerbation

The subject currently has or had an exacerbation in the past 4 weeks? No ☐ Yes ☐

Symptoms

1- ***How much fatique have you experienced in <u>the last four weeks</u> ?*** ☐

1- No fatigue at all
2- Some fatigue
3- Moderate fatigue
4- A lot of fatigue
5- Extreme fatigue

2- ***On an average day during <u>the past four weeks</u>,***

1- Nerver
2- A few times
3- Some times
4- Many times
5- All the time

a. How often have you **coughed** ? ☐
b. How often did you bring up **phlegm** ? ☐

3- ***On an average day during the past four weeks, how much shortness of breath did you have while :***

1- No shortness of breath
2- Very little shortness of breath
3- Moderate shortness of breath
4- A lot of shortness of breath
5- Extreme shortness of breath

a. Doing you **normal daily activities**. ☐
b. Performed activities that required you to raise your **arms overhead**. ☐
c. Walking on the level **at your own pace**. ☐

Feeling A

4- ***During the last four weeks, how often did the fear of becoming short of breath limit you in your activities of daily life ?*** ☐

1- All of the time
2- Many times
3- Some of the times
4- A few times
5- None of the time

5- ***On an average day in the past four weeks how often have you felt :***

	All of the time	Many of the times	Some of the times	A few times	None of the time
a. **Fringhtened or worried** about not being able to breathe.	1	2	3	4	5
b. **Frustrated** or impatient.	1	2	3	4	5
c. That everything seems **too much of an effort**.	1	2	3	4	5
d. **Unable to accept** your pulmonary condition.	1	2	3	4	5

Feeling B

These questions are about how you feel and how things have been with you during the past 4 weeks.
6 ***For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...***

	All the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	1	2	3	4	5
b. Have you been very nervous?	1	2	3	4	5

c. Have you felt downhearted and depressed?	1	2	3	4	5
d. Did you feel worn out?	1	2	3	4	5

7 ***How TRUE or FALSE is each of the following statements for you***

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. My health is excellent.	1	2	3	4	5

Physical Function A

8 ***Compared to a person your own age, how much more time does it take <u>you to perform your daily activities</u> ?***

1- Not at all longer
2- Somewhat longer
3- Moderately longer
4- Quite a bit longer
5- A lot longer

9 ***The following items are about activities you might do <u>during a typical day</u>. To what extend do your breathing problems now limit you in your ability to perform these activities ?***

	Not limited at all	Limited a little	Moderately limited	Limited a lot	Extremely limited
a. **Climbing a slope** or hill.	1	2	3	4	5
b. Getting **outside** the house.	1	2	3	4	5
c. **Going outside** on days which are hot/sunny, cold/damp or windy, or have elevated dust/pollution levels.	1	2	3	4	5
d. Being **autonomous** in your own home ie. not requiring any assistance.	1	2	3	4	5
e. Being able to **function sexually** (If sexual activity is not an issue for you, answer « not limited at all »)	1	2	3	4	5

Physical Function B

10 ***The following items are about activities you might do <u>during a typical day</u>. Does your <u>health now limit you</u> in these activities ? If so, how much ?***

	Not limited at all	Limited a little	Moderately limited	Limited a lot	Extremely limited
a. Climbing **one** flight of stairs.	1	2	3	4	5
b. Bending, kneeling, or stooping.	1	2	3	4	5
c. Walking **more than a kilometer**.	1	2	3	4	5

11 ***During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other daily activities <u>as a result of you physical health</u>?***

	All the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down the **amount of time** you spent on work or other activities	1	2	3	4	5
b. **Accomplished less** than you would like	1	2	3	4	5
c. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2	3	4	5

12 ***During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?***

1- Not at all
2- Slightly
3- Moderately
4- Quite a bit
5- Extremely

Time at the end of the questionnaire. : on 24:00

Boehringer Ingelheim

CASA-Q USER'S AGREEMENT

between Boehringer Ingelheim International GmbH, at Binger Str. 173, 55216 Ingelheim am Rhein, Germany (hereinafter "BOEHRINGER") and Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia, Jalan Yaacob Latiff, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia (hereinafter "Licensee").

BOEHRINGER hereby grants permission to the Licensee to employ the Cough and Sputum Assessment Questionnaire (CASA-Q) in a study entitled "A Randomised, Open Label, Interventional Study Evaluating the Efficacy & Safety of Dry Powder Ivy Extract (Syrup Prospan) Vs NAC among COPD Patients". Licensee will be supported by Delfi Marketing Sdn Bhd, Level 6, Block A, Sky Park One City, Jalan USJ 25/1, 47650 Subang Jaya, Selangor, Malaysia to perform the study. Study results will be owned by Licensee.

BOEHRINGER will supply the Licensee with the CASA-Q in its original version (US English) and currently available translations, as listed below.

none

The instrument will be administered on paper. The Licensee acknowledges that new translations must be carried out by ICON/MAPI.

The use of the CASA-Q in the above-mentioned study to the following conditions:

1. The study is intended to be performed with 120 patients.

   ☐ For commercial studies the permission to use the CASA-Q is granted with a royalty fee of US$ 5.00 per patient.

   The Licensee will pay a royalty fee in the amount of US$ 0.00 (nil USD) to BOEHRINGER for use of the CASA-Q in this study. Payment is due within 60 days upon signature of this Agreement by authorized representatives from both parties.

   ☐ Sponsors of new translations will be exonerated from the royalty fee. This means, the Licensee can use the existing translations in this study at no charge.

   ☑ The use of the CASA-Q in academic research or individual clinical practice is free of charge.

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3. The Licensee shall retain all rights to any data and/or results generated by the use of CASA-Q in the study.

4. The Licensee is free to publish any results of the study provided that Licensee does not publish any part of the CASA-Q and that all publications include the copyright clause as stated in Article 1.

5. This Agreement holds for the above-mentioned study only. The use of the CASA-Q in any additional study of the Licensee will require a separate agreement.

6. The license period dates from the Effective Date (date of last signature) to one (1) year after completion of the study.

7. Place of venue for all disputes arising in connection with this Agreement is Frankfurt. This Agreement is governed by German Law.

8. This Agreement may be executed in two or more counterparts, each of which shall be deemed an original and all of which shall together be deemed to constitute one agreement. The parties agree that execution of this Agreement by industry standard electronic signature software and /or by exchanging PDF signatures shall have the same legal force and effect as the exchange of original signatures. If any proceeding arising under or relating to this Agreement, each party hereby waives any right to raise any defense or waiver based upon execution of this Agreement by means of such electronic signatures or maintenance of the executed agreement electronically

Signed and dated by: 11-Jul-2023
Boehringer Ingelheim International GmbH

i.V.

DocuSigned by:
Dr. Karin Becker
CF728436EA07482...
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Dagmar Kaschinski

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Hospital Canselor Tuanku Muhriz

Associate Prof Dr Mohamed Faisal Abdul Hamid
Consultant Pulmonologist
Faculty of Medicine
Hospital Canselor Tuanku Muhriz
Universiti Kebangsaan Malaysia
11 July 2023

Section 14: References

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