Study Protocol

Perception, Adherence, Clinical, Economical and Health-Related Quality of Life Outcomes of CareAide® App usage in Chronic Diseases

Protocol number, version number and date:

Protocol number, Version 9.0, 30 July 2022

Name and Institution of Principal/Coordinating investigator:

Dr Ong Siew Chin, School of Pharmaceutical Sciences Universiti Sains Malaysia (USM), Penang Dr. Baharudin Ibrahim, Faculty of Pharmacy, Universiti Malaya, Malaysia

Professor Dr. Hasniza Binti Zaman Huri, Faculty of Pharmacy, Universiti Malaya, Malaysia

Name and Institution of Principal investigator at the Site:

Dr. Baharudin Ibrahim, Faculty of Pharmacy, Universiti Malaya, Malaysia

Dr. Navin Kumar A/L Loganadan, Hospital Putrajaya

Dr. Jaya Muneswarao A/L Ramadoo@Devudu, Hospital Pulau Pinang

Dr. Izyan Binti A Wahab, Faculty of Pharmacy, University of Malaya, 50603 Kuala Lumpur, Malaysia

Dr. Kayatri A/P Govindaraju, Faculty of Pharmacy, University of Malaya, 50603 Kuala Lumpur, Malaysia

Dr. Rajat Rana, Faculty of Pharmacy, University of Malaya, 50603 Kuala Lumpur, Malaysia

Ng Chow Kyn, Universiti Sains Malaysia, Malaysia

Mohamed Syamir, Faculty of Pharmacy, University of Malaya, 50603 Kuala Lumpur, Malaysia

Name and Institution of Sub/Co investigator at the Site:

Dato' Dr. Mohamed Jahangir bin Abdul Wahab, Hospital Pulau Pinang, Malaysia

Ho Shien Chee, Hospital Pulau Pinang, Malaysia

Name and address of Sponsor:

CaringUp Malaysia Sdn Bhd

8-1, Level 8, Menara CIMB. No.1, Jalan Stesen Sentral 2 Kuala Lumpur, Sentral 50470 Kuala Lumpur. Malaysia

Study site/s:

University Malaya Medical Centre, Kuala Lumpur

Hospital Putrajaya, Putrajaya

Hospital Pulau Pinang, Pulau Pinang

1.0 Introduction/Background

The prevalence of non-communicable diseases (NCDs) including diabetes, hypertension, heart failure and asthma is higher especially in the bottom income group. According to WHO and Ministry of Health (MOH) Malaysia 2020 report, expenditure for chronic diseases estimated involved around 0.65% of Malaysia's gross domestic product (GDP) which is about RM8.91 billion (Ministry of Health Malaysia, 2020). This showed that chronic diseases imposed a significant health burden to our country. Therefore, stakeholders and public should work together to identify the sources and curb the prevalence of chronic diseases from continuing to rise in Malaysia. Despite free access to essential medicines and health services in the public sector, health literacy remains poor, service uptake remains low, and medication non-adherence persists.

Adherence to therapies is a primary determinant of treatment success and is associated with improved clinical outcomes in the management of chronic diseases. Generally, the medication adherence rates are lower in chronic disease patients than in those with acute disease. Failure to adherence negatively affects the efficacy, safety and costs of therapies. According to the World Health Organization's (WHO's) 2003 report, 50% of patients with chronic diseases do not adhere to their prescribed treatment and identified non-compliance as global health crisis. Similarly, in Malaysia, despite the Malaysian population having good and easy access to effective medical therapy under the public healthcare system, approximately 46% to 56% of patients with hypertension were non-adherent in terms of their medications. Increasing medical adherence is, therefore, a public health priority.

The health ministry has tried various interventions aiming to improve medication adherence, including technical, behavioural, educational, social support and structural interventions. However, changing people's behaviours toward medication adherence can be challenging. To compound this problem, long-term care requires the active involvement of healthcare resources and is usually costly and labour-intensive. Thus, new and innovative approaches to changing the attitudes and behaviours regarding adherence are needed.

In Asia-Pacific countries, usually it is the families who are primarily and personally responsible for the healthcare of the patients due to the culture. Thus, it is crucial to include them as part of the solutions to the adherence issues. In the age of fourth industrial revolutions and the advancements of digital technologies, digital solutions such as applications ('apps') on

smartphones, are increasingly used in healthcare. Further, the extensive development of information and communication technologies characteristic of modern society enables interventions to reach large populations. CareAide® is a digital app that may help to manage complex medicine schedules and improve adherence thus help manage complex medicine schedules with minimal involvement of healthcare resources. The app can include both the patients and the caregivers to monitor the medication taking behavior.

Previous studies have shown the association of adherence and clinical outcomes in diabetes, hypertension, asthma and heart failure patients (Asche et. al. 2011; Chia et. al. 2021; Shang et. al. 2019; Vahatalo et. al. 2021). These studies have shown the improvement of glycaemic control, blood pressure, health care utilization, quality of life, mortality, cardiovascular events and asthma control with higher adherence. Therefore, by using the CareAide® app, we hypothesized that these important clinical and health-related quality of life outcomes will also be indirectly improved when the adherence increases.

Mobile health interventions have been proved to be cost-effective in the management of diabetes and hypertension in overseas studies (Li et al., 2021; Tsuji et. al., 2020; Purcell et al., 2014). However, a few systematic reviews found that the outcome for economic evaluation were inconsistent, and most studies reported applied simple platforms such as text messages or phone reminder (Beratarrechea et al., 2014, Iribarren et al., 2017; Li et al., 2020; Sanyal et al., 2018). Furthermore, there is little evidence regarding the economic evaluation of mobile health apps for improving chronic disease management in developing country such as Malaysia. Therefore, this study will also explore the economic impact of mHealth app (CareAide ®) in the management of chronic diseases among adults in Malaysia.

Despite the launch and its utility, it is important to understand how people perceive and use the digital app. The user satisfaction survey can provide a better understanding of users' perception of the CareAide® app. Through assessing users' perception and satisfaction with the app, it is possible to improve the design of future CareAide® app that is more effective and can tailor the features according to their needs. Therefore, this study also aims to gauge the perception and satisfaction of the CareAide® app. Findings from this study will be helpful for the app developers for revisiting their app features and services that can lead to continued use of the app.

2.0 Research Questions

1. Can CareAide® improve the medication adherence?

2. What is the clinical impact of CareAide® on chronic diseases?
3. What is the economical and HRQOL impact of CareAide®?
4. What is the users' perception on the CareAide® application?

3.0 Research Objective:

3.1 Primary Objective

1. To evaluate the effect of CareAide® intervention on adherence to medications in patients with chronic diseases.

3.2 Secondary Objectives

1. To determine the clinical outcomes of CareAide® usage in patients with chronic diseases.
2. To evaluate and determine the cost-effectiveness of CareAide® in the management of chronic diseases in Malaysia.
3. To study and assess the burden and health-related quality of life (HRQoL) of chronic diseases for estimation of the quality adjusted life years (QALY).
4. To gauge the users' perception and satisfaction of the CareAide® application.

4.0 Methodology

4.1 Study Design

A 3- and 6- month open-label multicentre randomized controlled trial with two parallel groups will be conducted. This study will take place in the outpatient setting of the three hospitals [i.e., Hospital Putrajaya, Hospital Pulau Pinang and Universiti Malaya Medical Center (UMMC)) in Malaysia]. Standard chronic disease treatments will be given to both groups of participants, but the CareAide ® app will be provided for the experimental group during the trial. Both groups will be allocated to 1:1 ratio. Randomization number will be generated by using online number generated programme. Consultants reviewing patients at medical, cardiology, diabetes mellitus and asthma clinics will provide referral and notify independent researchers for eligibility and group assignments. Eligible patients will then be instructed to see pharmacists/researchers at outpatient pharmacies to refill their prescriptions and subsequently enrol in the assigned study group either to receive an intervention with CareAide® or to receive normal clinical care. Information and training on the app will be provided by these researchers to the participants.

4.2 Participant Recruitment, Eligibility Criteria and Study Procedures

Patients will be recruited at the respective outpatient clinics. At the usual care clinic appointments, patients have their demographics and baseline data of blood pressure, blood sugar, basic blood profiles, asthma control and review of their disease management collected by consultants/researchers. Patients who meet the study criteria will then be instructed to see pharmacists/researchers at outpatient pharmacy to refill their medications. The pharmacists/researchers will screen patients' inclusion and exclusion criteria for this study and will explain that they may or may not be selected for the study and if they agree, proceed to provide written informed consent. The adherence data from the screening will be collected to gauge the general adherence rate in these group of patients. An independent researcher, who is not involved in the intervention and control groups, will use the random number function in Excel to generate randomisation sequences. The random numbers will be placed in opaque envelopes, which subsequently will be opened by pharmacists/researchers at the outpatient pharmacies. Participants and pharmacists/researchers are unblinded to group assignment and are aware of the intervention, but the study hypotheses are not disclosed to the participants. The assessor and statisticians are blinded to participant allocation. The study will be evaluating usual care compared with usual care plus pharmacist-driven patient-specific adherence interventions - CareAide® medication adherence digital application. Usual care provided by these hospitals comprises clinic appointments every 3 to 6 months.

4.2.1 Intervention group

- Intervention group will be asked to download and use the CareAide® app to help manage medications for 12 to 24 weeks. CareAide® is a free digital application designed to manage complex medicines schedules and improve adherence.

4.2.2 Control group

- Control group will not be asked to download any digital applications but only receive the usual care by the hospitals.

4.3 Patients' inclusion and exclusion criteria are as follow:

4.3.1 Inclusion criteria:

- Age: 18 years and above
- Diagnosed with selected non-communicable diseases (NCDs): hypertension, diabetes mellitus, heart failure or asthma for at least 6 months
- Prescription generated from one of the following specialty clinics: Medical, Cardiology, Diabetes Mellitus or Asthma clinics
- Medications are prescribed in previous 3 months and refill at the point of recruitment
- Morisky Medication Adherence Scale (MMAS) score < 6
- More than three medications daily or two medications with multiple dosing intervals.
- One or more hospital admissions in the prior 24 months
- Understand and able to command in English and own a smartphone

4.3.2 Exclusion criteria:

- Medications prescribed from other institution providers
- Existing mobile health app or medication reminder app user
- Pregnant
- Cognitively impaired
- Prisoners
- Bed-bound
- Severe diseases/comorbidities – terminal cancer, psychiatry, etc

4.3.3 Withdrawal criteria:

Participants can choose to withdraw at any time for any reason, specified or unspecified, and without prejudice to their care. Participants may be withdrawn if the investigator feels that it is not for the participants' best interest to continue. The following is a list of possible reasons for study intervention discontinuation:

- Screening failure

- Participant withdrawal of consent
- Participant is not compliant with study procedures
- Protocol violation requiring discontinuation
- Lost to follow-up
- Request from sponsor for early termination of study
- Participant death

Withdrawn participants will not be replaced. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the Case Report Form (CRF). The Investigator will contact participants who are lost to follow-up. Contacts attempts with such subjects will be documented in the participant's records (e.g., times and dates of attempted phone contact, receipt for mailing a registered letter, etc.).

4.4 Outcome measurements

4.4.1 Phase 1

4.4.1.1 Primary outcome

Medication adherence: CareAide® effectiveness is measured with a medication adherence tool at baseline and follow-up time periods at 3 months and 6 months using Morisky Medication Adherence Scale-8 (MMAS-8) and proportion of days covered (PDC). The primary outcome of the study is medication adherence, which is assessed using the 8-item Morisky Medication Adherence Scale (MMAS-8) and the Proportion of Days Covered (PDC) method. Measurements are taken at baseline and at two additional time points, with a 3-month interval following the intervention. MMAS-8 is a licensed validated questionnaire to assess medication adherence, where a higher score represents higher medication adherence and vice versa. Comprising of 8 items, the score ranges from 0 to 8, where a higher score represents a higher medication adherence. The internal consistency (Cronbach's alpha) of MMAS-8 is 0.83 along with a sensitivity of 93% and a specificity of 57%. The PDC method utilises pharmacy refill records (Raebel et al., 2013). The PDC can be calculated as below (Hess et al., 2006; Raebel et al., 2013; Pednekar et al., 2019):

Nm/Nd x 100%

Where Nm denotes the number of days covered by the medication while Nd meant the number of days in the study period. The patients are considered to be adherent if their PDC scores are ≥0.8 or 80% (Karve et al., 2009). The prescription refill data was extracted from outpatient/hospital database.

4.4.1.2 Secondary outcomes

Fasting blood sugar, HbA1C, cardiovascular events (heart failure admission, mortality), asthma control and blood pressure, hospitalizations and emergency visits measurements will be based on the clinics attended by the participants. Health care utilization, quality of life and health care expenditures will be measured for all the participants.

i. Data Collection

Data on patients' sociodemographic, resources consumptions such as direct and indirect medical costs and health quality of life (HRQoL) will be collected.

ii. Sociodemographic

Data such as socio-demographics (age, sex, education level, occupation, income, and religion), will be collected via face-to-face interview or phone interview via a structured and validated questionnaire.

iii. Direct Medical Cost

This study will apply a bottom-up micro costing approach for direct cost estimation. Healthcare costs such as outpatient visits, medicine use, hospitalization, diagnostic and laboratory test costs will be gathered in this study for direct cost estimation of chronic diseases. Costs for outpatient visits, hospitalization, diagnostic and laboratory tests will be valued based on the MOH Full Paying Patient Tariff Schedule of fees for a foreigner patient scheme provided by the Financial Department for Ministry of Health Hospitals. Medication utilization costs will be estimated from the National Price List of Medicines provided by the Procurement Unit of the Pharmacy Department. Costs of medicine per patient will be calculated by total drugs supplied for a patient multiplied by the average acquisition cost price obtained of the hospital. All costs will be valued in Malaysia Ringgit (MYR).

iv. Indirect Medical Cost

Indirect medical or patient out-of-pocket cost such as transportation costs, productivity losses, caregiver costs and waiting time in outpatient visit will be collected with the used of cost questionnaires to the participants. Patients will be requested to report the resource utilization over the past 3 months during the first time after recruitment(baseline) and after every 3 months (at 3 and 6 months). Transportation costs included parking fees. Patient time costs will be calculated based on waiting time in outpatient visit with the wages per hour of patient. Rate of wages per hour will be estimated based on patient's reported income per hour. Productivity losses will not be accounted for patients who are retired and jobless. This economic cost will help to evaluate the economic impact of CareAide from patients' perspective. All costs will be valued in Malaysia Ringgit (MYR).

v. Health-related quality of life (HRQoL) of patients

The overall health state and quality of life will be collected with the EuroQol-5D (EQ-5D-5L) and Short Form 36 Health Survey (SF-36) questionnaires to determine quality-adjusted life years (QALYS) over 3- and 6- months follow-up time. This study will use the EQ-5D-5L and SF-36 surveys to assess the HRQoL of chronic disease patients. The EQ-5D-5L instrument of the EuroQol is a validated tool to measure the health status of various groups in various diseases. This tool composed of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/ depression (Lins et. al., 2016). Another questionnaire SF-36 is a self-reported measure of health with 36 items which cover eight domains of health. The eight domains including vitality, mental health, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning and social role functioning (Lins et al., 2016). Both tools consist of questionnaires whereas EQ-5D-5L consists of additional visual analogue scale. These tools will be conducted via face-to face or phone interview to assess the health status of respondents.

Trained research personnel will explain the purpose of the study and obtain consent of the participants before distributing or administering the questionnaires. Participants will then be distributed with questionnaires. EQ-5D-5L and SF-36 have different languages versions of the validated phone interview or face-to face questionnaires included English, Malay, Tamil and

Chinese languages for Malaysians. Research personnel will provide or use the patients' preferred version of language for conducting the survey.

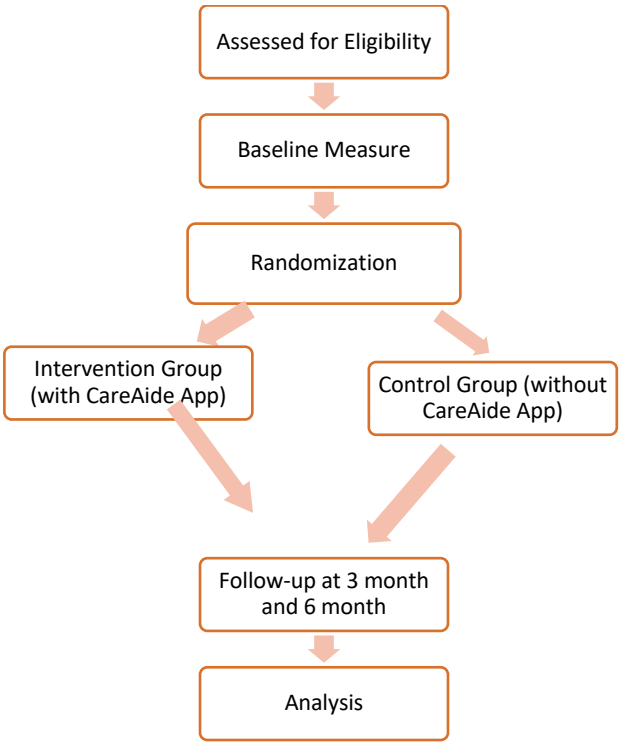

Figure 1: Consolidated Standards of Reporting (CONSORT) flow chart (Consort, 2021; Evsenbach et. al., 2011).

4.4.2 Phase 2

Only the participants using the CareAide® app will be given the questionnaires at the end of 6 months follow up to understand the participant's perception of the perceived usefulness of the app and rate their satisfaction with the app. A structured questionnaire will be developed from existing literature (Kim et al., 2016; Eveleth & Robert, 2020) to facilitate data collection. It will be designed to be self-administered. The questionnaire will be divided into three sections to specify the type of questions to be asked. The first section consists of basic demographics, including age, gender, ethnicity, personal health status, and the number of medications taken. Section two includes the questions to explore the perception of the users towards the app. The responses will be measured using a 5-point Likert scale. Section three consists of a questionnaire to rate their satisfaction with the app.

For perception, the perceived usefulness questions were developed from the work of Kim et al., 2016), and the self-efficacy questions will be developed from Eveleth & Robert, (2020). The ratings will be given on a 5-point Likert scale. A higher rating corresponds to the higher agreement (e.g., 1=strongly disagree, 5=strongly agree).

For satisfaction, the satisfaction questionnaire will be an adaptation of the user satisfaction survey used in the mobile health (mHealth) apps by Melin et al. (2020). The questionnaire consists of 11 questions, 10 items where the respondent will be asked to rate to what extent they agree on each item on a 5-point Likert scale and concluded with an open question on the recommendation of any suggestions to customise the experience to the patient's needs.

Data will be collected via a self-administered questionnaire to explore the study participants´ perceptions and satisfaction with the CareAide® app. The self-administered questionnaires will either be mailed or given in person to the respondents, and their participation is entirely voluntary. The content validity of the questionnaire will be assessed by a panel of experts based on their evaluation analysis through comments and feedback submitted. The questionnaire will be pilot tested on 20 patients to check the feasibility and validity of the questionnaire. Results from the pilot study will not be included in the final analysis. Should the respondents fail to understand and answer the questionnaire, modifications will be done to obtain accurate data. Cronbach's alpha test will be used to assess the internal consistency of the questionnaire.

Section 1: Participant demographics

Age group, gender, ethnicity, phone type, health status, education level, and number of medications taken

Section 2: Perception of perceived usefulness of the CareAide® app

i. Improves medication adherence
ii. Makes remote patient monitoring possible and easy
iii. Improves the chance patients take their medications properly and on time - Excellent reminder to take or refill patient prescriptions and track pills remaining.
iv. Improves social performance - Patients interaction with mobile apps (whether is clear and understandable)

v. Practicality of technology for elderly (technology laggards, novice users or lack of comfort and familiarity with smartphones).

Section 3: Participant Satisfaction with the CareAide® app

a) What did you think about using the health app? (5-point Likert scale)

- It was easy to use
- It was good to use
- The time spent using it has been acceptable
- The introduction of how to use it was sufficient
- It was too time-consuming
- It was boring to use
- It was a disturbance/ distraction
- I will recommend it to others

b) Do you have any suggestions about how the app could do better and customise the experience for your needs?

_____

4.5 Sample Size

The primary outcome for this study is to assess medication adherence of patient after using mobile health application. Therefore, sample size for this randomized controlled trial is calculated using the continuous outcome formula below (Charan & Biswas, 2013; Wittes, 2002):

$$n_i = \frac{2(Z\alpha_{/2} + Z_\beta)^2 P\,(1-P)}{(P_1 - P_2)^2}$$

$n_{i=}$ sample size required for each group $(i = 1,2)$

$Z\alpha_{/2}$= Assumed type I error: α equal to 5%, then $Z_{0.05_{/2}} = Z_{0.025} = 1.96$ (From Z table)

Z_β= Assumed power of 80% Z_β=0.84

$P_1 - P_2$= Effect Size= Difference in the proportion of events in two groups

P= Total prevalence

Total Sample size needed: 388 per group

Note: Based on few past studies reported for non-adherence rate for patients in Malaysia is within 46.6% to 56% (Ting et al., 2019). Therefore, assumption of prevalence of chronic disease is 70%

of the adult and adherence rate of 50% is made. A systematic review showed that mobile app able to improve adherence by 7% to 40% (Pérez-Jover et al., 2019). Medication non-adherence rate of 50% is expected in control group and 40% is expected in intervention group. For a 10% absolute difference in medication non-adherence rate between control and intervention group, 388 patients per arm should be recruited in the study assuming a type I error of 5% and power of 80%.

N (number to enrol) * (1-% drop out) = desired sample size

Therefore N (number to enrol) = desired sample size / (1- % drop out)

N= 388/0.80= 485 per group

Based on a systemic review published by Wood and colleagues found out there is a possibility of 20% loss of follow-up, drop out and those who are unable to meet the inclusion criteria (Wood et al., 2004). Therefore, a minimum sample size of 970 is needed in this study, with the number of 485 in each arm.

The sample size obtained from the primary outcome is too large and which might need to spend more time and manpower. Hence, the sample size calculation is repeated with the use of secondary outcome which is cost-effectiveness economic evaluation of the study. Glick (2011) formula is applied for the calculation of sample size as it incorporates all important economic evaluation informations such as difference in treatment costs and effects and willingness to pay threshold in a single formula.

$$n_i = \frac{2\left(Z_{\alpha/2} + Z_{\beta}\right)^2 \left(Sd_C{}^2 + \left(W^2 Sd_Q{}^2\right) - \left(2\,W\,p\,Sd_C\,Sd_Q\right)\right)}{(W\Delta Q - \Delta C)^2}$$

$n_{i=}$ sample size required for each group ($i = 1,2$)

$Z_{\alpha/2}$= Assumed type I error: α equal to 5%, then $Z_{0.05/2} = Z_{0.025} = 1.96$ (From Z table)

Z_{β} = Assumed power of 80% Z_{β}=0.84

W = Willingness to pay threshold

p = Expected correlation between difference in costs (ΔC) and effects (ΔQ)

ΔQ = Expected difference in mean effects

ΔC = Expected difference in mean costs

Sd_Q = Expected standard deviation for the effects

Sd_C = Expected standard deviation for the costs

To our knowledge, there is no published study has evaluated the direct and indirect costs and quality of life associated with mobile health app for the management of non-communicable diseases. Therefore, the calculation is based on the assumption and few literature results. According to a study published in Malaysia, RM 2499.15 is required for the managing of patient complicated with diabetes and heart failure after the first event (Shafie & Ng, 2020). The cost from the study is adjusted according to Consumer Price Index 2022. The cost difference between treatment group is considered as around 30% as reported by the use of mobile app in the management of heart failure study (Cano Martín et al., 2014). A minimum difference of 0.01 is estimated in term of QALY in favour of mobile health app user. Sd_C and Sd_Q are assumed as RM1000 and 0.01 respectively. The willingness to pay threshold is set at RM 28,470 per QALY as reported by Lim et al. (2017). The correlation coefficient is set at minimum 0.1 as estimated from cost-effectiveness analysis of a mobile-based intervention for patients with type 2 diabetes mellitus conducted by Li et al. (2021). A number of 150 patients (75 per study group) is required to detect at least 80% power assuming a two-tailed test and alpha of 5% between treatment group. The sample size will be rounded up to 200 patients to account for a possibility of 20% attrition. The sample size obtained is corresponding to the sample size applied in Li et al. (2021) cost-effectiveness analysis study.

4.6 Data Analyses

Intention to treat (ITT) analysis will be applied to evaluate the results to avoid any bias. The data analysis will be using the SPSS version 27. Data will be coded and analysed. Descriptive or categorical data will be expressed as mean ± standard deviation (SD) unless otherwise stated. Student t-test will be used for analysis of normally distributed or continuous variables. Mann-Whitney test will be used for non-normally distributed data. Categorical data will be analysed using Chi-square or Fischer's exact test. A value of $P < 0.05$ is considered statistically significant.

The prevalence of medication compliant is quantified at 3 months and 6 months follow-up. Independent t-test or Mann-Whitney test will be used to compare MMAS score rankings between the intervention and control groups. Chi-Square test of independence will be used to determine the difference in number of patients with medication adherence between the intervention and control groups at 3 months and 6 months follow-up. Ordinal logistic regression, with the MMAS adherence score ranking, will be used to examine the association between intervention and control groups.

For the perception and satisfaction towards the app, the frequency and percentage of respondents in each category (strongly disagree to strongly agree) will be calculated. The median of each statement will then be calculated to give an overview of perception and satisfaction towards the CareAide® app. Chi-square, Mann-Whitney U, Kriskall Wallis, Chi-square tests and logistic regression will be used where appropriate. The open-ended question will be analysed using thematic analysis as proposed by Braun and Clarke (2012). Codes will be assigned to the data to describe the content. After the coding is completed, themes will be generated, reviewed, and named. Linear regression analysis will be conducted to determine the independent predictors of HRQoL.

An economic evaluation will be conducted from a payer and societal perspective. Costs and outcomes will be discounted at 3% per year (Shafie et al., 2019) as the results will be extrapolated to examine costs and outcome over a year.. Cost effectiveness analysis will be estimated based on the results of cost data and EQ-5D-5L to calculate the incremental cost per quality adjusted life year (QALY) gained. Total incremental cost effectiveness ratio (ICER) will be calculated by dividing the difference between the cost of CareAide intervention group and control group by the difference between the QALYs of CareAide intervention group and control group. Sensitivity analysis will be performed by bootstrapping technique to ensure or examine the robustness of ICER. Then, cost effectiveness acceptability curve (CEAC) will be created to estimate the proportion of the result being cost-effective in relation to the Willingness-to-Pay (WTP) threshold.

4.7 Risk and Benefit to study participants

The study contributes minimal or no risk to the participants. This study may improve the medication adherence for participants.

4.8 Risk Benefit Assessment

As stated above, this study contributes minimal or no risk to the participants. As this study involves questionnaire survey, participants are requested to spend 15 to 30 minutes to complete questionnaires carefully and truthfully.

4.9 Ethical Consideration

For government hospitals, ethical approval will be sought from the Medical Research Ethics Committee (MREC), meanwhile PPUM-MREC will be sought for PPUM research site.

5.0 Conflict of Interest

There is no conflict of interest to declare.

5.1 Privacy and Confidentiality

Data will be kept at Universiti of Malaya (UM). Primarily only investigators in the study will have access to the research data. However, individuals involved in this sub-study, qualified monitors and auditors, the sponsor or its affiliates and governmental or regulatory authorities may inspect and copy research, where appropriate and necessary. Any unused sample that has not been processed in research will be destroyed. Information that was extracted from medical records will not be destroyed until 7 years after the last publication. Results that will be obtained from this study will be published, presented, and shared with other researcher, scientist and community. In Caringup system, the user (patient/family) data is owned by the user. The user can delete their data at any time. The data from all the repositories can be erased as bounded by the General Data Protection Regulation (GDPR). The personal data will be encrypted and stored in Microsoft Azure cloud. A user (patient or family members) will get Data Privacy Policy in English and Malay when signing up to use CareAide app. No data will be transmitted from hospitals such as UMMC, Hospital Putrajaya and Hospital Pulau Pinang to CaringUp company. The data of the patients who participate in the study will be provided by CaringUp to research team. Patient data is owned by patient. They can delete at any time according to the regulation.

5.2 Publication Policy

No personnel information will be revealed, and subjects will not be identified when the findings of the results are published. Permission from the Director General of Health, Malaysia will be obtained prior to publication.

5.3 Termination of Study

The sponsor may decide to terminate the study at any time if there is sufficient reasonable cause. Circumstances that may warrant termination or suspension such as lack of recruitment, inability

to sustain or further manage the study or due to safety concerns. Participants will be informed if the study is terminated and follow-up visits will be arranged if needed.

References

Asche, C., LaFleur, J., & Conner, C. (2011). A review of diabetes treatment adherence and the association with clinical and economic outcomes. Clin Ther, 33(1), 74-109. https://doi.org/10.1016/j.clinthera.2011.01.019

Baker-Eveleth, L., & Stone, R. W. (2020). User's perceptions of perceived usefulness, satisfaction, and intentions of mobile application. International Journal of Mobile Communications, 18(1), 1-18.

Beratarrechea, A., Lee, A. G., Willner, J. M., Jahangir, E., Ciapponi, A., & Rubinstein, A. (2014). The impact of mobile health interventions on chronic disease outcomes in developing countries: a systematic review. Telemed J E Health, 20(1), 75-82. https://doi.org/10.1089/tmj.2012.0328Charan, J., & Biswas, T. (2013). How to Calculate Sample Size for Different Study Designs in Medical Research. Indian Journal of Psychological Medicine, 35(2), 121-126.

Cano Martín, J. A., Martínez-Pérez, B., de la Torre-Díez, I., & López-Coronado, M. (2014). Economic impact assessment from the use of a mobile app for the self-management of heart diseases by patients with heart failure in a Spanish region. Journal of medical systems, 38(9), 1-7.

Chia, Y. C., Devaraj, N. K., Ching, S. M., Ooi, P. B., Chew, M. T., Chew, B. N., Mohamed, M., Lim, H. M., Beh, H. C., & Othman, A. S. (2021). Relationship of an adherence score with blood pressure control status among patients with hypertension and their determinants: Findings from a nationwide blood pressure screening program. The Journal of Clinical Hypertension, 23(3), 638–645.

Consort - The CONSORT Flow Diagram. (2021). Retrieved 11 December 2021, from http://www.consort-statement.org/consort-statement/flow-diagram.

Eysenbach, G. (2011). CONSORT-EHEALTH: Improving and Standardizing Evaluation Reports of Web-based and Mobile Health Interventions. Journal Of Medical Internet Research, 13(4), e126. doi: 10.2196/jmir.1923.

Glick, H. A. (2011). Sample size and power for cost-effectiveness analysis (part 1). *Pharmacoeconomics*, *29*(3), 189-198. https://doi.org/10.2165/11585070-000000000-00000

Iribarren, S. J., Cato, K., Falzon, L., & Stone, P. W. (2017). What is the economic evidence for mHealth? A systematic review of economic evaluations of mHealth solutions. PloS one, 12(2), e0170581.

Islam, S., Peiffer, R., Chow, C., Maddison, R., Lechner, A., & Holle, R. et al. (2020). Cost-effectiveness of a mobile-phone text messaging intervention on type 2 diabetes—A randomized-controlled trial. Health Policy and Technology, 9(1), 79-85.

Kim, S. C., Yoon, D., & Han, E. K. (2016). Antecedents of mobile app usage among smartphone users. Journal of marketing communications, 22(6), 653-670.

Li, J., Sun, L., Hou, Y., & Chen, L. (2021). Cost-Effectiveness Analysis of a Mobile-Based Intervention for Patients with Type 2 Diabetes Mellitus. Int J Endocrinol, 2021, 8827629. https://doi.org/10.1155/2021/8827629

Li, R., Liang, N., Bu, F., & Hesketh, T. (2020). The Effectiveness of Self-Management of Hypertension in Adults Using Mobile Health: Systematic Review and Meta-Analysis. JMIR Mhealth Uhealth, 8(3), e17776.

Lim YW, Shafie AA, Chua GN, Hassali MAA (2017). Determination of CostEffectiveness Threshold for Health Care Interventions in Malaysia. Value in Health, 20(8), 1131-1138.

Lins, L., & Carvalho, F. M. (2016). SF-36 total score as a single measure of health-related quality of life: Scoping review. SAGE open medicine, 4, 2050312116671725.

Melin, J., Bonn, S. E., Pendrill, L., & Trolle Lagerros, Y. (2020). A Questionnaire for Assessing User Satisfaction with Mobile Health Apps: Development Using Rasch Measurement Theory. JMIR mHealth and uHealth, 8(5), e15909.

Ministry of Health Malaysia. (2020). The impact of noncommunicable diseases and their risk factors on Malaysia's gross domestic product. Retrieved 9 December 2011, from https://www.moh.gov.my/index.php/database_stores/attach_download/554/64

Pérez-Jover, V., Sala-González, M., Guilabert, M., & Mira, J. J. (2019). Mobile Apps for Increasing Treatment Adherence: Systematic Review. Journal of medical Internet research, 21(6), e12505.

Purcell, R., McInnes, S., & Halcomb, E. J. (2014). Telemonitoring can assist in managing cardiovascular disease in primary care: A systematic review of systematic reviews. BMC Family Practice, 15(1), 43. https://doi.org/10.1186/1471-2296-15-43

Sanyal, C., Stolee, P., Juzwishin, D., & Husereau, D. (2018). Economic evaluations of eHealth technologies: A systematic review. PLoS One, 13(6), e0198112.

Shafie, A. A., Fen, N. C., Shabaruddin, F. H., Din, R. M., Yen, L. S., & Lajis, R. et al. (2019). Pharmacoeconomic Guidelines Malaysia Second Edition 2019.

Shafie, A. A., & Ng, C. H. (2020). Estimating the costs of managing complications of type 2 diabetes mellitus in Malaysia. *Malaysian Journal of Pharmaceutical Sciences*, *18*(2), 15-32.

Shang, P., Liu, G. G., Zheng, X., Ho, P. M., Hu, S., Li, J., Jiang, Z., Li, X., Bai, X., & Gao, Y. (2019). Association between medication adherence and 1-year major cardiovascular adverse events after acute myocardial infarction in China. Journal of the American Heart Association, 8(9), e011793.

Ting, C., Adruce, S., Loo, S., Ting, H., & Tnay, J. (2019). Interventions on Improving Medication Adherence in Malaysia: A Mini Review. Journal Of Young Pharmacists, 11(2), 122-125.

Tsuji, S., Ishikawa, T., Morii, Y., Zhang, H., Suzuki, T., Tanikawa, T., Nakaya, J., & Ogasawara, K. (2020). Cost-Effectiveness of a Continuous Glucose Monitoring Mobile App for Patients with Type 2 Diabetes Mellitus: Analysis Simulation. J Med Internet Res, 22(9), e16053. https://doi.org/10.2196/16053

Vahatalo, I., Kankaanranta, H., Tuomisto, L. E., Niemela, O., Lehtimaki, L., & Ilmarinen, P. (2021). Long-term adherence to inhaled corticosteroids and asthma control in adult-onset asthma. ERJ Open Res, 7(1). https://doi.org/10.1183/23120541.00715-2020

Wittes, J. (2002). Sample Size Calculations for Randomized Controlled Trials. Epidemiologic Reviews, 24(1), 39-53.

Wood, A. M., White, I. R., & Thompson, S. G. (2004). Are missing outcome data adequately handled? A review of published randomized controlled trials in major medical journals. Clinical trials, 1(4), 368-3.

PATIENT INFORMATION SHEET AND INFORMED CONSENT FORM
(for adult subjects and interventional studies)

1. **Title of study**: Perception, Adherence, Clinical, Economical and Health-Related Quality of Life Outcomes of CareAide® App usage in Chronic Diseases

2. **Name of investigator and institution:**

   a. Dr. Ong Siew Chin (Pincipal/Coordinating Investigator)
   b. Associate Professor Dr. Baharudin Ibrahim (Pincipal Investigator at University Malaya Medical Centre, Kuala Lumpur)
   c. Associate Professor Dr. Hasniza Binti Zaman Huri (Co/Sub Investigator at University Malaya Medical Centre, Kuala Lumpur)
   d. Dr. Navin Kumar A/L Loganadan (Principle Investigator at Hospital Putrajaya, Putrajaya)
   e. Dr. Jaya Muneswarao A/L Ramadoo@Devudu (Principle Investigator at Hospital Pulau Pinang, Pulau Pinang)

3. **Name of sponsor**: CaringUp Malaysia Sdn Bhd

4. **Introduction:**

   You are invited to participate in a research study because you have chronic disease that requires on long term medication treatment. CareAide® is a digital app that may help to manage complex medicine schedules and improve adherence thus help manage complex medicine schedules with minimal involvement of healthcare resources. The app can include both the patients and the caregivers to monitor the medication taking behavior. The details of the research trial are described in this document. It is important that you understand why the research is being done and what it will involve. Please take your time to read through and consider this information carefully before you decide if you are willing to participate. Ask the study staff if anything is unclear or if you like more information. After you are properly satisfied that you understand this study, and that you wish to participate, you must sign this informed consent form. To participate in this study, you may be required to provide you doctor with information on your health history; you may harm yourself if you are not truthful with the information provided.

   Your participation in this study is voluntary. You do not have to be in this study if you do not want to. You may also refuse to answer any questions you do not want to answer. If you volunteer to be in this study, you may withdraw from it at any time. If you withdraw, any data collected from you up to your withdrawal will still be used for the study. Your refusal to participate or withdrawal will not affect any medical or health benefits to which you are otherwise entitled.

   This study has been approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia.

5. **What is the purpose of the study?**

The purpose of this study is to evaluate and determine the effect and clinical outcome of CareAide® intervention on adherence to medications in patients with chronic diseases. Besides, this study is also designed to evaluate cost-effectiveness of this intervention by assessing the burden and health related quality of life of the patient with chronic disease. Last but not least, the users' perception and satisfaction of the CareAide® application will also be gauged and reviewed in this study. This research is necessary because chronic diseases imposed a significant health burden to our country. Many studies found that the medication adherence rates are lower in chronic disease patients than in those with acute disease. Failure to adherence negatively affects the efficacy, safety and costs of therapies. New and innovative technology such as mobile health application, CareAide® should be applied to improve medication adherence of patient in managing their chronic diseases which in turn to improve patient health status.

This research will be conducted for the duration of 3 years (Jan 2022 until Dec 2024) and your participation will be around 6 months. The expected number of participants is 970 individuals from Malaysia.

6. What kind of study products will I receive?

If you agree to participate in the study, you will be instructed to see pharmacists/researchers at outpatient pharmacies to refill their prescriptions. The pharmacists/researchers will screen for the inclusion and exclusion criteria for this study and will explain that the you may or may not be selected for the study and if you agree, proceed to provide written informed consent. You will be subsequently enrolled in the assigned study group either to receive an intervention with CareAide® or to receive normal clinical care. An independent researcher, who is not involved in the intervention and control groups, will use the random number function in Excel to generate randomisation sequences. The random numbers will be placed in opaque envelopes, which subsequently will be opened by pharmacists/researchers at the outpatient pharmacies. You have equal chance of being assigned to each of the groups.

The study product is a mobile health application. You will be provided information and training about the app if you are in the group to receive and intervention with CareAide®.

Group 1: Patient will be asked to download and use the CareAide® app to help manage medications for 12 to 24 weeks. CareAide® is a free digital application designed to manage complex medicines schedules and improve adherence.

Group 2: Patient will not be asked to download any digital applications but only receive the usual care by the hospitals.

7. What will happen if I decide to take part?

Study Procedures

If you agree to be in this study, you will undergo some activities, test and evaluations to determine if you are eligible for this study. Such tests and evaluations are completed during a screening period that takes place before participation in the main part of the study. Please refer to the study activities table below.

Study Activity Table:

	Screening/ Assess for Eligibility	**Baseline Assessment and Randomization**	**Follow Up at 3 Month**	**Follow Up at 6 Month**
Visit	1	2	3	4
Timeline (at weeks)	-1	0	12	24
Procedures				
Screen Inclusion and Exclusion Criteria	X			
Informed Consent	X			
Randomization		X		
Subjects Demographics		X		
Medical History		X		
Medication History		X	X	X
Laboratory data		X	X	X
Vital Signs (Blood Pressure, Heart Rate etc.)		X	X	X
Physical Exam (ECG etc.)		X	X	X
Direct and indirect cost		X	X	X
Medication Adherence Asssessment (Morisky Medication Adherence Scale, Proportion of Days Covered)		X	X	X
Health Related Quality of Life (HRQoL)		X	X	X
Perception of the perceived usefulness of the app and rate your satisfaction of the app				X

Screening Visit / Assess for Eligibility

You will be referred by consultants at the respective outpatient clinics if you meet our study criteria during consultation period. You will then be instructed to see pharmacists/researchers at outpatient pharmacies to refill their prescriptions and will be screened for inclusion and exclusion criteria for this study. You will be provided a written informed consent if you are selected and agreed to participate in this study.

Baseline Visit and Randomization

If you pass Screening, your demographics and baseline data of blood pressure, blood sugar, basic blood profiles, asthma control and review of your disease management will be collected by consultants/researchers.

Following that you will be randomly assigned by chance. An independent researcher, who is not involved in the intervention and control groups, will use the random number function in Excel to generate randomisation sequences. The random numbers will be placed in opaque envelopes, which subsequently will be opened by pharmacists/researchers at the outpatient

pharmacies. You will be subsequently enroll in the assigned study group either to receive an intervention with CareAide® or to receive normal clinical care. Information and training on the app will be provided by these researchers to the participants.
Besides, you will be given a questionnaire form to be answered. This form contains few sections which will enquire and assess about your direct and indirect cost estimation, medication adherence and Health Related Quality of Life (HRQoL). These few sections are to assess for the 3 months prior to randomization or this study. For direct medical cost, you will be requested to report the cost of visiting and medication obtained from facility other than your current recruited facility. You will be required to declare the indirect cost such as cost of transportation, productivity losses, caregiver costs and waiting time in outpatient visit. Morisky Medication Adherence Scale (8-Item) questionnaire will be used to assess your medication adherence. Moreover, you will be requested to fill up EQ-5D-5L and SF-36 surveys to assess your HRQoL.

Follow Up Visit At 3 Months
This is the first follow up visit of the study, which is 3 months after the intervention allocation. You will be assessed for fasting blood sugar, HbA1C, cardiovascular events (heart failure admission, mortality), asthma control and blood pressure.
Besides, you will be given a questionnaire form to be answered. This form contains few sections which will enquire and assess about your direct and indirect cost estimation, medication adherence and Health Related Quality of Life (HRQoL) over the last 3 months.

Follow Up Visit At 6 Months
This is the last follow up visit of the study, which is 6 months after the intervention allocation. You will be assessed for fasting blood sugar, HbA1C, cardiovascular events (heart failure admission, mortality), asthma control and blood pressure.
Besides, you will be given a questionnaire form to be answered. This form contains few sections which will enquire and assess about your direct and indirect cost estimation, medication adherence and Health Related Quality of Life (HRQoL) over the last 3 months.
You will be given the questionnaires at the end of 6 months follow up to assess your perception of the perceived usefulness of the app and rate your satisfaction with the app if you are allocated to Group and using the CareAide® app.

8. When will I receive the trial product and how should it be kept?

You will be asked to download and use the CareAide® app throughout the 6 months period of the study if you are assigned to Group 1. The study staff will instruct you on how to download and manage the app. In contrast, you will not be asked to download any digital applications but only receive the usual care by the hospitals if you are assigned to Group 2.

9. What are my responsibilities when taking part in this study?

It is important that you answer all of the questions asked by the study staff honestly and completely which will take about 30 minutes of your time. Study team will also access your medical records for the following information:
1. Patient's Data

2. Direct Healthcare Cost Estimation (Outpatient follow up visits, Inpatient admission, Intensive care unit admission, Emergency admission, others community care services, laboratory investigation test, medications history)
3. Pharmacy Refill Record

You will be given a questionnaire form to be answered. This form contains 6 sections which will enquire about your demographic data, disease state, direct and indirect cost estimation, Morisky Medication Adherence Scale (8-Item), perceptions of the use of CareAide® App and Health Related Quality of Life (HRQoL).

10. What kind of treatment will I receive after my participation in the trial?

No study product will be given to you at the end of your participation in the study. Whether you complete the study or withdraw early, your usual care and treatment for chronic disease still received from hospital.

11. What are the potential risks and side effects of being in this study?

Participation to this study will not affect your treatment, and the risk is minimal. You are free to decline to answer any of the questions that you feel uncomfortable with.

12. What are the benefits of being in this study?

There may or may not be any benefits to you. You will not be reimbursed or paid for participation in this study. Information obtained from this study will help to evaluate and determine the effect and clinical outcome of CareAide® intervention on adherence to medications in patients with chronic diseases. This study also helps to estimate the direct and indirect cost of managing chronic diseases in Malaysia and how this app able to reduce the economic burden from payer and societal perspective. Furthermore, it is able to understand the health-related quality of life of patients in management of chronic diseases.

13. What if I am injured during this study?

If you are injured as a result of being in this study, you should contact your study investigator. In the event of a bodily injury or illness directly resulting from the study product or a medical procedure required for this study, the sponsor will pay for reasonable and necessary treatment. The sponsor is not responsible for medical expenses due to pre-existing medical conditions, any underlying diseases, any ongoing treatment process, your negligence or willful misconduct, the negligence or willful misconduct of your study doctor or the study site or any third parties. You do not lose any of your legal rights to seek compensation by signing this form.

14. What are my alternatives if I do not participate in this study?

You do not have to participate in this study to get treatment for your disease or condition. This study will not affect your treatment options.

15. Who is funding the research?

This study is sponsored by CaringUp Malaysia Sdn Bhd who will pay for study product (mobile health application) and data collection procedure. All other drugs and procedures that are not required by the study but are part of your routine medical care will have to be paid by you or your insurance.

16. Can the research or my participation be terminated early?

The study doctor or the sponsor may due to concerns for your safety, stop the study or your participation at any time. If the study is stopped early for any reason you will be informed and arrangements made for your future care. You may be asked to attend a final follow-up visit.

17. Will my medical information be kept private?

All your information obtained in this study will be kept and handled in a confidential manner, in accordance with applicable laws and/or regulations. Permission from the Director General of Health, Malaysia will be obtained prior to publication. When publishing or presenting the study results, your identity will not be revealed without your expressed consent. Primarily only investigators in the study will have access to the research data. However, Individuals involved in this sub-study, qualified monitors and auditors, the sponsor or its affiliates and governmental or regulatory authorities may inspect and copy research, where appropriate and necessary. Any unused sample that has not been processed in research will be destroyed. Any information that was extracted from medical records will not be destroyed until 7 years after the last publication of findings using your information. Moreover, the staffs will inform you in a timely manner about any new findings or changes about the study product which may affect your health or willingness to continue in this study. Where necessary, you may be asked to reconsent to participate.

18. Who should I call if I have questions?

If you have any questions about the study or if you think you have a study related injury and you want information about treatment, please contact study investigator at site:
Hospital Pulau Pinang: 012-2239848 (Dr. Jaya Muneswarao A/L Ramadoo@Devudu)
Hospital Putrajaya: 012-6653893 (Dr. Navin Kumar A/L Loganadan)
University Malaya Medical Centre: 010-3664181 (Associate Professor Dr. Baharudin Ibrahim)

If you have any questions about your rights as a participant in this study, please contact: The Secretary, Medical Research & Ethics Committee, Ministry of Health Malaysia, at telephone number 03-3362 8407 / 8205 / 8888

INFORMED CONSENT FORM

Title of Study: Perception, Adherence, Clinical, Economical and Health-Related Quality of Life Outcomes of CareAide® App usage in Chronic Diseases

By signing below I confirm the following:

- I have been given oral and written information for the above study and have read and understood the information given.
- I have had sufficient time to consider participation in the study and have had the opportunity to ask questions and all my questions have been answered satisfactorily.
- I understand that my participation is voluntary and I can at anytime free withdraw from the study without giving a reason and this will in no way affect my future treatment. I am not taking part in any other research study at this time. I understand the risks and benefits, and I freely give my informed consent to participate under the conditions stated. I understand that I must follow the study doctor's (investigator's) instructions related to my participation in the study.
- I understand that study staff, qualified monitors and auditors, the sponsor or its affiliates, and governmental or regulatory authorities, have direct access to my medical record in order to make sure that the study is conducted correctly and the data are recorded correctly. All personal details will be treated as STRICTLY CONFIDENTIAL
- I will receive a copy of this subject information/informed consent form signed and dated to bring home.
- I agree/disagree* for my family doctor to be informed of my participation in this study. *(*delete which is not applicable)*

Subject:

Signature: I/C number:

Name: Date:

Investigator conducting informed consent:

Signature: I/C number:

Name: Date:

Impartial witness: *(Required if subject is illiterate and contents of patient information sheet is orally communicated to subject)*

Signature: I/C number:

Name: Date:

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
(*MEDICAL RESEARCH & ETHICS COMMITTEE*)
KEMENTERIAN KESIHATAN MALAYSIA
MINISTRY OF HEALTH MALAYSIA
Kompleks Institut Kesihatan Negara (NIH)
No.1, Jalan Setia Murni U13/52,
Seksyen U13 Bandar Setia Alam,
40170 Shah Alam, Selangor. Tel: 03-3362 8398/8399/8404/8408

Ref : 22-01108-COI
Date : 29-August-2023

ONG SIEW CHIN
HOSPITAL PULAU PINANG

NAVIN KUMAR A/L LOGANADAN
HOSPITAL PUTRAJAYA

JAYA MUNESWARAO
HOSPITAL PULAU PINANG

BAHARUDIN BIN IBRAHIM
UNIVERSITI MALAYA SPECIALIST CENTRE

Dato'/ Dr. / Tuan/ Puan,

Annual Ethical Renewal for 2023

NMRR ID-22-01108-COI (IIR)
Protocol No :
Perception , Adherence, Clinical, Economical and Health-Related Quality of Life Outcomes of CareAide® App usage in Chronic Diseases

2. With reference to the 'Continuing Review Form' submitted **19-July-2023**, we are pleased to inform that the conduct of the above study has been granted approval (via Full Board Review) for a year by the Medical Research & Ethics Committee, Ministry of Health Malaysia. For next renewal of ethical approval, a completed 'Continuing Review Form' must be submitted to MREC **within 2 months (60 days)** before the expiry of the approval.

3. The Medical Research & Ethics Committee, Ministry of Health Malaysia operates in accordance with The International Council for Harmonization of Technical Requirement for Pharmaceutical for Human Use (ICH) and Malaysia Guidelines for Good Clinical Practice.

Ref : 22-01108-COI
Date : 29-August-2023

Effective date: 29-August-2023 Until 28-August-2024

Comments (if any): NIL

“MALAYSIA MADANI”

“BERKHIDMAT UNTUK NEGARA”

Yours sincerely,

.....
(DR NURAIN MOHD NOOR)
Chairman
Medical Research & Ethics Committee
Ministry of Health Malaysia

Ref : 22-01108-COI
Date : 29-August-2023

MEMBERS OF THE MEDICAL RESEARCH & ETHICS COMMITTEE WHO ATTEND THE MEETING ON 29 AUGUST 2023

No	NAME	GENDER	EXPERTISE	DESIGNATION/ AFFILIATION	ROLES	TICK (√) IF PRESENT
1	**MREC Chairperson** Dr Nurain Mohd Noor	F	Endocrinology	Putrajaya Hospital	Medical reviewer	X
2	**Deputy Chairperson** Dr Ami Fazlin Syed Mohamed	F	Clinical Pharmacology	Institute of Medical Research	Medical reviewer	√
3	**Deputy Chairperson** Dr Tang Swee Ping	F	Paediatric Rheumatology	Hospital Selayang	Medical reviewer	X
4	**Secretary** Dr Lee Keng Yee	F	Bioethics	National Institute of Health (NIH)	MREC Secretary	√
5	Dr Salina Abdul Aziz	F	Psychiatry & Clinical Epidemiology	-	Medical reviewer (Independent Member)	√
6	Datin Dr Noriah Bidin	F	Public Health	-	Medical reviewer (Independent Member)	√
7	Dr Asiah Kassim	F	Paediatric Respiratory	Tunku Azizah Hospital	Medical reviewer	√
8	Dr. Tan Hui Siu	F	Bioethics & Paediatric	Hospital Ampang	Medical reviewer	√
9	Datuk Dr Nor Fariza Ngah	F	Ophthalmology	Hospital Shah Alam	Medical Reviewer	X
10	Dr Noraziani Khamis	F	Public Health	Institute of Health Management	Medical Reviewer	X
11	Dr Malini A/P S. Shanmuganathan	F	Health Research Ethics	Institut Penyelidikan Klinikal	Medical reviewer	√
12	Dr. Sharifah Naiemah Syed Mansor	F	Emergency	Hospital Selayang	Medical reviewer	√

Ref : 22-01108-COI
Date : 29-August-2023

No	NAME	GENDER	EXPERTISE	DESIGNATION/ AFFILIATION	ROLES	TICK (√) IF PRESENT
13	Dr. Charlotte Jane Joseph	F	Developmental Paeds	Hospital Tunku Azizah	Medical reviewer	√
14	Dr Yuslina Mat Yusoff	F	Pathology	Institut Penyelidikan Perubatan	Medical reviewer	√
15	Dr Asral Wirda Ahmad Asnawi	F	Pathology Haematology	Universiti Sains Islam Malaysia (USIM)	Medical Reviewer (Independent Member)	X
16	Dr Hazdalila Yais Haji Razali	F	Legal	UITM	Medical Reviewer (Independent Member)	√
17	Dr Mohammad Zabri Johari	M	Public Health Psychology, social research methodology, mixed methods research	Institute of Health Behavioural Research	Scientific Reviewer	√
18	Ms Chun Geok Ying	F	Pharmacy	Clinical Trial Unit (CTU), Hospital Ampang	Scientific reviewer	X
19	Dr Lean Qi Ying	F	Pharmacy, Business Administration	Universti Teknologi Mara, Kampus Pulau Pinang	Scientific Reviewer (Independent Member)	√
20	Prof Dr Wee Lei Hum	F	Health Education	Taylor's University	Scientific Reviewer (Independent Member)	X
21	Dr Wan Rosalina Wan Rosli	F	Pharmacology	University of Cyberjaya	Scientific Reviewer (Independent Member)	√
22	Dr Caryn Chan Mei Hsien	F	Psychology	UKM, KL Campus	Scientific Reviewer	√

No	NAME	GENDER	EXPERTISE	DESIGNATION/ AFFILIATION	ROLES	TICK (√) IF PRESENT
					(Independent Member)	
23	Malisanurhidayu Yaacob	F	Biomolecular Sciences / Nutritional Sciences	Pusat Darah Negara	Scientific Reviewer (Independent Member)	X
24	En. Abu Hurairah Bahari	M	-	-	Lay person (Independent Member)	√
25	En. Lim Teng Ann	M	-	-	Lay person (Independent Member)	√
26	En Mohd Hadziq Mohd Zafari	M	-	Hospital Pakar Kanak-Kanak, UKM	Lay person (Independent Member)	X
27	Sharina Md Nasri	F	-	National Institute of Health (NIH)	MREC SEC Members	X
28	Mah Kar Yee	F	Pharmacy	National Institute of Health (NIH)	MREC SEC Members	√
29	Dr Zaril Harza bin Zakaria	M	Pharmacy	NPRA	Independent Expert (Non-voting member)	X

The Medical Research & Ethics Committee, Ministry of Health Malaysia operates in accordance to the International Council for Harmonization of Technical Requirement for Pharmaceutical for Human Use (ICH). Any member of the MREC who is involved in the study / project under review will not participate in the approval of the study / project.

UNIVERSITY OF MALAYA MEDICAL CENTRE

MEDICAL RESEARCH ETHICS COMMITTEE
(Formerly known as Medical Ethics Committee)
UNIVERSITY OF MALAYA MEDICAL CENTRE

ADDRESS : LEMBAH PANTAI, 59100 KUALA LUMPUR, MALAYSIA
TELEPHONE : 03-79493209/2251 FAXIMILE : 03-79492030

NAME OF ETHICS COMMITTEE/IRB Medical Research Ethics Committee, University Malaya Medical Centre	**MREC ID NO**: 2022311-11069
ADDRESS : LEMBAH PANTAI, 59100 KUALA LUMPUR, MALAYSIA	
PROTOCOL NO(if applicable) : 1	
TITLE: Perception, Adherence, Clinical, Economical And Health-Related Quality Of Life Outcomes Of Careaide® App Usage In Chronic Diseases	
PRINCIPAL INVESTIGATOR : HASNIZA BINTI ZAMAN HURI	**SPONSOR** Caring Up Malaysia Sdn Bhd

The following item [✓] have been received and reviewed in connection with the above study to conducted by the above investigator.

[✓] Application for Amendment/Notification to Research Project (form)	Ver.No : -	Ver.Date : 15-09-2022
[ ] Annual Study Report/Study Closure Report	Ver.No : -	Ver.Date : -
[ ] Serious Adverse Event Report	Ver.No : -	Ver.Date : -
[✓] Other documents		
	Ver.No : -	Ver.Date : 27-09-2022

and the decision is [✓]

[✓] Approved (Expedited)

[ ] Approved (Full Board)

[ ] Rejected (reasons specified below or in accompanying letter)

[ ] Noted

Comments:

-

The investigators are required to:

1) *follow instructions, guidelines and requirements of the Medical Research Ethics Committee.*
2) *report any protocol deviations/violations and any serious unexpected adverse events related to the conduct of the study or study product to Medical Research Ethics Committee.*
3) *provide annual and closure report to the Medical Research Ethics Committee.*
4) *comply with International Conference on Harmonization – Guidelines for Good Clinical Practice (ICH-GCP) and Declaration of Helsinki.*
5) *obtain a permission from the Director of UMMC to start research that involves recruitment of UMMC patient.*
6) *ensure that if the research is sponsored, the usage of consumable items and laboratory tests from UMMC services are not charged in the patient's hospital bills but are borne by research grant.*
7) *note that he/she can appeal to the Chairman of Medical Research Ethics Committee for studies that are rejected.*
8) *note that Medical Research Ethics Committee may audit the approved study.*
9) *ensure that the study does not take precedence over the safety of subjects.*

Date of expedited approval : 11-10-2022

Date of notification : -

This is a computer generated letter. No signature required.