STUDY PROTOCOL

PROTOCOL TITLE:
The Impact of Bilingual Prescription Medication Labels on Medication Adherence and Medication Management Self-Efficacy Among Elderly Singaporeans: A Pilot Study

PROTOCOL NUMBER:
1

PROTOCOL VERSION: 3
PROTOCOL DATE: 10 September 2021

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Table of Contents

PROTOCOL SIGNATURE PAGE

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Sponsor Name:
Population-based, Unified, Learning System for Enhanced and Sustainable Health Centre Grant (PULSES CG)

Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP).

Principal Investigator Name: Khee Giat Yeng

Principal Investigator Signature: 

Date: 10 September 2021

1. BACKGROUND AND RATIONALE

Elderly, an at-risk group: Life expectancy among the elderly is rising globally, including Singapore.[1] A longer life places the elderly at risk of chronic diseases, which often entail long term drug therapy.[2] The elderly, thus, with their co-morbidities, have a higher risk of polypharmacy, which in turn is associated with a greater likelihood of medication non-adherence.[3] Further, given their exposure to polypharmacy, **the elderly often have to navigate through multiple PMLs** on a daily basis.

Prescription Medication labels (PMLs): PMLs, affixed on packets/bottles of prescription medications, are the **patients' main source of medication-related instructions in Singapore**. Many patients in Singapore receive no information from healthcare providers except the instructions on PMLs, further highlighting their relevance.[4] Correct understanding of PMLs is key to medication safety and adherence,[5-7] esp. for the elderly.[8] Difficulty in finding and comprehending information on PMLs can adversely affect patient safety and adherence to instructions.[9] Although local data on medication errors attributed to PML misunderstanding are lacking, a study elsewhere reported that majority of outpatient medication errors are due to patients' inability to take their own medications as intended[10]. And, poor medication safety and adherence result in poor clinical outcomes and unnecessary healthcare costs.[11] **Thus, ensuring that patients, esp. the elderly, correctly understand their PMLs is vital.**

A key barrier faced by elderly Singaporeans in reading and understanding their PMLs is the language commonly used on them, English. A study of a national sample of elderly Singaporeans found that despite 69% being unable to read English, their PMLs were mostly only in English (81%).[12] This discrepancy places the elderly at risk of medication errors, non-adherence, and side effects. At the same time, many elderly Singaporeans who cannot read English can read another official language (Mandarin Chinese/Malay/Tamil).[13] This highlights a **direct and innovative approach to make existing PMLs patient-centric**, i.e., add another preferred language – **bilingual PMLs**. A study led by the project mentor showed that bilingual PMLs lead to a substantial increase in understanding of PML content among the elderly, supporting its real-world utility.[12,14] And, patient feedback collated by the project Co-Is (SGH pharmacists) strongly suggests the need for bilingual PMLs. However, adoption of bilingual PMLs in Singapore has been slow. One reason is the lack of evidence for their positive impact on important medication-related outcomes, i.e., medication management self-efficacy and medication adherence. **The proposed study will provide rich preliminary data that will enable the conduct of a larger RCT on the impact of bilingual PMLs on these very medication-related outcomes.**

Conceptual Framework: Our framework focuses on the relationship between attainment of knowledge (medication knowledge via PMLs), medication management self-efficacy and engagement in self-care behaviours (i.e. medication taking behaviour) as a process that ultimately affects our key outcome, medication adherence. **(Figure 1)**

Attainment of knowledge: Cognitive processes (i.e., perception, memory, problem solving, etc.) generally subsume the concept of understanding.[15] In investigating PML understandability, understanding has been defined as the capacity to describe – using one's own words (i.e., more than simply reading) – how a medication should be taken.[16] In context of our study, bilingual PMLs will facilitate understanding among the elderly, resulting in attainment of medication knowledge. Research shows that lack of knowledge is likely to affect individual's self-

Figure 1: Conceptual framework

efficacy to adhere to complex regimens.[17,18] Further, it has been suggested that interventions aimed at improving medication adherence should design interventions targeted at increasing knowledge and self-efficacy.[19]

Medication management self-efficacy: Self-efficacy, drawing on the social-cognitive theory, is defined as "the individual's belief in their capabilities to implement a specific/a set of behaviour(s)".[20] More specifically, in context of medication management, self-efficacy refers to a belief in the patient's capacity to follow a prescribed medical regimen when faced with challenging situations.[21] Several studies have found a positive link between medication management self-efficacy and medication adherence.[22] Self-efficacy directly affects health behaviours.[23] Patients with higher self-efficacy are more likely to have better adherence to self-care tasks, such as medication taking.[24,25]

Medication adherence: Adherence to medications is critical to ensuring optimal health outcomes, yet around 50% of patients do not do so.[26] In the United States, up to two-thirds of all medication-related hospitalizations result from poor medication adherence. Singaporean data also portrays low medication adherence rates.[27,28] Medication adherence is influenced by patient, physician, medication and health-system factors.[29] **Our study, by initiating evidence gathering for the impact of bilingual PMLs on medication adherence, concurrently addresses two such factors, a patient factor, i.e., language reading ability, and a health-system factor, particularly important in Singapore, i.e., PMLs.**

Overall, we conceptualise that by facilitating attainment of medication knowledge (better understanding via bilingual PMLs), patients will advance their medication management self-efficacy, leading to engagement in medication taking behaviour, ultimately resulting in medication adherence.

Need for rigorous PML intervention studies: A recent review on the impact of improved PMLs concluded that **intervention studies that test PML improvements in a rigorous manner are lacking**.[30] It also recommended that future studies should **extend research to outcomes more proximal to medication taking** – medication adherence and medication management self-efficacy. In Singapore, the only published PML intervention did show bilingual PMLs (vs English PMLs) to increase PML understanding.[12] However, it, again, did not assess medication adherence and medication management self-efficacy. **Thus, rigorous intervention studies that assess the impact of improved PMLs on a range of medication-related outcomes are needed.**

Our proposal is the *first step* towards a well-informed, rigorous intervention study or RCT that will provide concrete evidence on the impact of the provision of bilingual PMLs on key medication-related outcomes – medication adherence, medication management self-efficacy, and PML understanding. The experience gained, and data collected, through the conduct of the 2 pilot trials, funded through the current proposal, will allow us to choose the optimal trial design, and refine protocols for recruitment, engagement and retention of study participants for the larger RCT as well as determine variability in outcomes so that the larger RCT is appropriately powered to detect meaningful differences in the outcomes – an immediate output of our proposed project will be a grant proposal to a national level grant mechanism for the conduct of the larger RCT. **Eventually, the 2 pilot trials, and the subsequent larger RCT, will contribute to implementing patient-centered PMLs.**

2. HYPOTHESIS AND OBJECTIVES

Since the proposed study will collect preliminary data for informing the larger RCT, it does not aim to detect a significant difference in the trial outcomes in either pilot trial. Rather, its specific aims are:

AIM 1. To assess the feasibility of administering the intervention in the 2 "pilot" RCT versions. The proposed formative study will inform which of the 2 pilot trials will be scaled up and tested in the larger RCT. It will also result in finalization of the intervention and measurement material.
AIM 2. To refine protocols for study participant recruitment, engagement and retention.
AIM 3. To gain experience with and refine measurement of the medication-related outcomes.

A key outcome, medication adherence, will be measured using several approaches – self-report (ARMS[31,32]; MedTake Assessment[33]), which is easier and cheaper[34], and objective (pill count[35]; electronic medication packaging [EMP][36]), which is tedious and expensive – during the 2 pilot trials. Comparison of the various approaches against the EMP (the most objective approach) will inform the choice of the measurement approach to be used for medication adherence in the larger RCT.

3. EXPECTED RIKS AND BENEFITS

Risks to participants are expected to be minimal in the study:

(1) Potential risk from breach of confidentiality: Exposure of patient-related information such their personal details and medical information (including medication they are taking, medication-adherence scores)

Expected benefits are as follows:

(1) Improved medication-related outcomes: Provision of bilingual PMLs through the study is expected to improve the following 3 areas for participants- medication adherence, medication management self-efficacy, and PML understanding. Improvements in these 3 areas will enhance the benefits patients will receive from their medication therapy, resulting in greater medication-related outcomes.

4. STUDY POPULATION

4.1. List the number and nature of subjects to be enrolled.

A total of 40 patients will be recruited from Singapore General Hospital's outpatient clinics, which is the only study site involved. There will be no subject restrictions based on race of the subject, but as per the inclusion criteria set out in section 4.3 below, they should be able to speak English and/or Mandarin, and unable to read in English but able to read Mandarin (as they will benefit the most from bilingual PMLs).

4.2. Criteria for Recruitment and Recruitment Process

Patients who meet all the inclusion criteria set out in section 4.3 below and do not meet any of the exclusion criteria set out in section 4.4 below are eligible to be recruited into the study. Suitable patients will be identified by either the patient's primary physician or by a pharmacist at Diabetes and Metabolism Centre (DMC) pharmacy. These suitable patients will be introduced to the study and if they express interest, they will be referred to the research assistant for consent taking, administration of the baseline covariate questionnaire and randomisation to study group.

4.3. Inclusion Criteria

(1) Singapore Chinese citizen/permanent resident; (2) age ≥50 years; (3) just received a new (i.e., not received before) oral medication for a chronic disease from DMC pharmacy; (4) no moderate/severe cognitive impairment (≥5 correct responses on the Abbreviated Mental Test, AMT); (5) not deaf (self-reported); (6) no binocular presenting near vision impairment (near visual acuity, with routinely used spectacles/lenses: at least 6/15 (0.40 logMAR) on the Landolt's C chart); (7) able to speak English and/or Mandarin; (8) unable to read in English but able to read Mandarin (as they will benefit the most from bilingual PMLs); (9) assessed as non-adherent as per 2 questions - " In the last one month, how often did you take your medications as prescribed by the doctor?" and "At times do you forget to take your prescription medications?" (as they will benefit the most from an intervention aimed at improving medication adherence).

4.4. Exclusion Criteria

(1) Patients who received, from the prescribing physician, a set of instructions for their new oral medication that does not match standard instructions (as the bilingual instructions for non-standard instructions would not be prepared for beforehand)

5. STUDY DESIGN AND PROCEDURES/METHODOLOGY

This is a 2-arm open-label parallel-group RCT with 2 versions (Pilot Trial A, and Pilot Trial B). A total of 40 eligible patients, after informed consent, will be randomized (1:1; block randomization, block of 4) in the DMC pharmacy to either Pilot Trial A or Pilot Trial B (Figure 2).

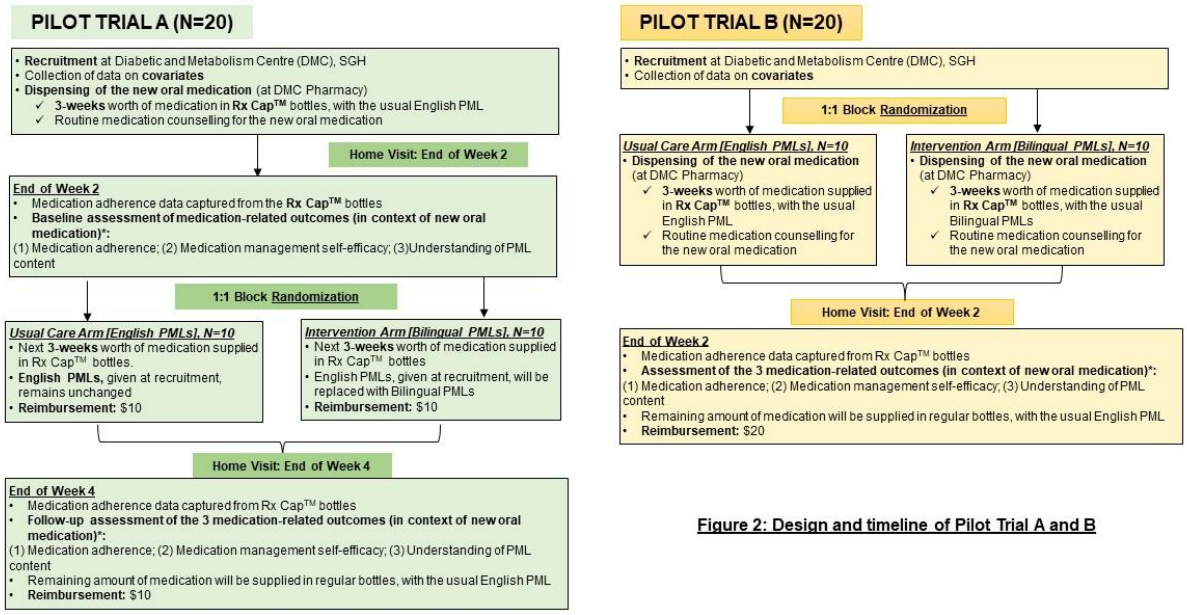

Figure 2: Design and timeline of Pilot Trial A and B

* Study procedures have been modified slightly in view of prevailing COVID-19 control measures. Please refer to section 5.1.1 for a detailed methodology.

5.1 Study Design

Briefly, in Pilot Trial A, all will be first given the usual English PML for their new medication. There may be non-standardized, ad-hoc noting on the PML by the pharmacy staff when participant is deemed not able to understand the English PML. All content of the non-standardized, ad-hoc noting including pictures drawn will be recorded. Then, ***at 2 weeks post-recruitment***, their baseline level of the 3 medication-related outcomes (w.r.t. the new medication) will be gauged, after which they will be ***randomized*** (1:1; block randomization, block of 4) to one of 2 PMLs (Bilingual [intervention] or English [usual care]) at their home. Follow-up assessment of the 3 medication-related outcomes will be also be done at 2 weeks post-randomization at their home.

In Pilot Trial B, participants will be ***randomized*** (1:1; block randomization, block of 4) ***just after recruitment*** to one of 2 PMLs (Bilingual [intervention] or English [usual care]) in the DMC pharmacy. There may be non-standardized,ad-hoc noting on the PML by the pharmacy staff when participant is deemed not able to understand the English PML. All content of the non-standardized, ad-hoc noting including pictures drawn will be recorded. The 3 medication-related outcomes will be assessed at 2 weeks post-randomization at their home.

All participants will receive their usual medical care, and usual medication counselling at the DMC pharmacy for all their medications. All medications, other than the new oral medication (which made them eligible, and whose PML will be intervened upon), will be dispensed with usual English PMLs.

5.1.1 Modified Study Design In View Of COVID-19

In view of COVID-19 restrictions imposed as of 16 August 2021, a portion of the Main Questionnaire will be done via phone call instead of fully relying on home visits. The study staff

will conduct a home visit to complete the remaining questions from the Main Questionnaire and collect data from the Rx Cap™ bottles, with a time limit of 20 minutes to keep participants and staff safe.

Additionally, should any participants be subjected to COVID-19 Stay Home Notices or Quarantine Orders, participation will immediately be forfeited for the safety of participants and study staff. Retrieval of the Rx Cap™ bottle and delivery of remaining medicines will be arranged in a proper manner in accordance to any guidelines set by the SGH Research Office and MOH.

5.2 Study Methodology

Bilingual PMLs (Intervention): Bilingual PMLs, for common medications at the DMC pharmacy, which "mirror" medication instructions on the corresponding English PMLs, will be developed by the investigator team. While the Health Products (Therapeutic Products) Regulations 2016 mandate English PML provision, there is no restriction to adding another language.[37] In fact, some polyclinics already print PMLs in their patients' preferred language, upon request, to supplement English PMLs.[38]

Randomization: All 3 block randomization sequences (Pilot Trial A or B, then, study arm within each Pilot Trial) will be generated a priori. After a participant gives consent, project staff will be informed of his/her allocation to Pilot Trial A or B. For those in Pilot Trial A, further assignment to study arm will be disclosed only after the baseline level of the 3 medication-related outcomes is assessed at 2 weeks post-recruitment. For those in Pilot Trial B, assignment to study arm will be disclosed immediately, as there is no baseline assessment of the 3 medication-related outcomes.

Covariates: A range of socio-demographic and medication-related (e.g. no. of medications, help received in medication management) variables will be collected, using a questionnaire, at recruitment.

Medication-related outcomes: They will be gauged at 2 weeks post-recruitment and 2 weeks post-randomization for those in Pilot Trial A, and at 2 weeks post-randomization for those in Pilot Trial B.

5.2.1 Measurements

Medication adherence: It will be measured in 4 different ways:

1. Adherence to Refills and Medications Scale (ARMS)[31,32]: A validated self-reported medication-adherence scale intended for patients with chronic diseases. The 12-item questionnaire consists of 2 sub scales - adherence to refilling prescriptions and adherence with taking medications. Each item is structured using the Likert scale, with the following response options and corresponding scores: "none" (score of 1), "some" (score of 2), "most" (score of 3), or "all of the time" (score of 4). The range of possible total scores is 12 to 48. Lower scores indicate better adherence.
2. MedTake Assessment[33]: A self-reported measure, recommended by Ministry of Health, Singapore for pharmacy staff when they provide pharmaceutical care services,[39] that assesses patient adherence and knowledge to dose, dosage, indication, food or water co-ingestion, and regimen. A composite score (0–100%; higher ~ better) summarizes patient's ability to take medication safely.
3. Pill count[40]: A pill count, in context of the new oral medication, will be done.
   % adherence= ((quantity dispensed)-(quantity remaining))/((prescribed number of pills per day)×(no.of days between dispensing date and interview))

Electronic medication packaging [EMP]: All participants will be dispensed their new oral

medication in a Rx Cap™ medication bottle (www.rxcap.com), whose Rx Cap™ Bluetooth smart cap will automatically track medication usage every time it is opened. Project staff will sync participants' data, collected and stored within the Smart Cap, at each home visit, and import it to the Rx Cap™ Engage platform for analysis. Continuous (% adherence to prescribed regimen; 0-100%) and categorical variables (not at all; partially; fully) for medication adherence will be derived. Rx Cap™ medication bottle is not being used in standard clinical practice yet and it is used for this proposed research only. To our best knowledge, Rx Cap™ medication bottle is not validated for use clinically yet.

Medication management self-efficacy: The 8-item Medication Understanding and Use Self-Efficacy Scale (MUSE), comprising 2 subscales – (1) taking medication (4 items), and (2) learning about medication (4 items), will be used. Item scores (four-point Likert scale; strongly disagree (score=1), to, strongly agree(score=4)) will be summed for subscale (range: 4-16) and total (range: 8-32) scores.[41]

PML understanding: It will be assessed by asking questions adapted from a local study[12] (led by the mentor) assessing this construct among elderly Singaporeans. Respondents will be asked tailored questions (in their preferred language) specific to the instructions presented on their PML for the new oral medication, for instance "How many times a day do you have to take this medication?". Each question will be marked as "correct" or "incorrect". Continuous (% correct responses; 0-100%) and categorical variables (none; partial; complete) for PML understanding will be derived.

5.2.2 Other Factors

Potential Difficulties/Alternative Approaches: ((1) Each respondent will be compensated with $20 worth of shopping vouchers as fair reimbursement for incidental expenses incurred for participating. The reimbursement can indirectly address potential recruitment issues by helping assuage any logistic issues the potential participants may have. (2) While we aim to recruit elderly who can read Mandarin, we may be limited by the language competency of the project staff. Nevertheless, we will try and arrange for conversant staff from other studies to supplement data collection. (3) The potential improvements to PMLs to be drawn from the expected findings may not directly address the needs of the elderly who are completely illiterate or have severe visual/cognitive impairment. Nonetheless, the pilot trials and subsequent RCT will benefit a large proportion of Singaporean elderly.

Withdrawals: Participants are free to withdraw their consent and discontinue their participation at any time without prejudice to him/her or effect on his/her medical care. However, the data that have been collected until the time of participant's withdrawal will be kept and analysed, to enable a complete and comprehensive evaluation of the study.

The study team may stop a participant's participation in the study at any time for one or more of the following reasons:

- Failure to follow the instructions of the Principal Investigator and/or study staff.
- The Principal Investigator decides that continuing the participant's participation could be harmful.
- The study is cancelled.

When a participant's participation in the study is withdrawn or stopped, their medications will be switched out from the Rx Cap™ bottle to the usual twist-cap amber bottles or ziplock bags that is provided by SGH Pharmacy. For those randomized to receive bilingual PMLs, their bilingual

PMLs will be switched out to the usual English PMLs that are provided by SGH Pharmacy.

6. SAFETY MEASUREMENTS

6.1. Definitions

Serious adverse event (SAE) in relation to human biomedical research, means any untoward medical occurrence as a result of any human biomedical research which:

- results in or contributes to death
- is life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in or contributes to persistent or significant disability/incapacity or
- results in or contributes to a congenital anomaly/birth defect
- results in such other events as may be prescribed

Adverse event (AE) in relation to human biomedical research means any untoward medical occurrence as a result of any human biomedical research which is NOT serious. Adverse event can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease possibly/ probably/ definitely associated with the participant in the human biomedical research.

6.2. Collecting, Recording and Reporting of Serious Adverse Events (SAEs) to CIRB

Only related SAEs (definitely/ probably/ possibly) will be reported to CIRB. Related means there is a reasonable possibility that the event may have been caused by participation in the research. Please refer to the CIRB website for more information on Reporting Requirement and Timeline for Serious Adverse Events.

The investigator is responsible for informing CIRB after first knowledge that the case qualifies for reporting. Follow-up information will be actively sought and submitted as it becomes available.

Related AEs will not be reported to CIRB. However, the investigator is responsible to keep record of such AEs cases at the Study Site File.

6.3. Safety Monitoring Plan

The PI, Co-Is, and study team will monitor and report any serious adverse events to the CIRB. As the study is expected to pose less than minimal risk to participants, the research team, overseen by the Principal Investigator, will perform data and safety monitoring. Research staff will ask participants about potential serious adverse events and more commonly known adverse events of their newly prescribed oral medication during their follow-up home visits.

6.4. Complaint Handling

Any complaints will be directed to the research team for investigation, and overseen by the Principal Investigator.

We will adhere to prevailing COVID-19 control measures as recommended by the SGH Research Office

7. DATA ANALYSIS

7.1. Data Quality Assurance

All data collected on hardcopy survey forms will be transcribed into electronic data using double data entry by two different individuals and verified for consistency. Any discrepancies will be resolved by referring to source documents. Only study team members will handle and access these data.

7.2. Data Entry and Storage

All data with personal identifiers will be encrypted with password-protection. All physical research data including consent forms, data entry forms will be stored in locked cabinets at SGH. All soft copy research data will be coded, with participants' identifiers stored separately from research data, and only available on computers within the institution. Only de-identified data will be shared with study team members for data analysis and only the investigators and authorized personnel (principal investigator, co-investigators and research assistant) directly involved with the study will have access to the data. After study completion, research data will be stored on institution computers and remain password-protected, for a minimum of 7 years after completion of research study or date of publication of the research using the research data, whichever is later.

The Rx Cap™ bottle measures patients medication adherence (Adherence is considered "met" when the new oral medication is taken based on both prescribed number of times per day and prescribed time of the day), each participant will be given 1-2 Rx Cap™ pill tracker bottles. The electronic cap of the pill tracker records the date and time when the patient opens the vial to take his/her medication. This bottle does not collect any personal identifiers. A Rx Cap™ account would be created for each participant. However, these accounts will be created by the study team using non-identifiable user information (i.e., "dummy" email addresses/usernames). As such, no personal identifiers will be stored in third-party databases.

8. SAMPLE SIZE AND STATISTICAL METHODS

8.1. Determination of Sample Size

Sample size/ power calculation is an important component for a RCT. However, as the proposed study is to conduct two pilot versions of a RCT, aiming to obtain preliminary data that will inform the sample size/ power calculation of a following, larger RCT, no sample size estimation has been done for the proposed study.

8.2. Statistical and Analytical Plans

As we are conducting 2 "pilot" versions of a RCT, most analyses will be descriptive and exploratory. In both pilots, trial outcomes will be summarized using measures of central tendency and dispersion (e.g., mean and standard deviation). In Pilot Trial A, significant difference in change, from baseline to 2 weeks post-randomization, in the 3 medication-related outcomes between the 2 arms will be assessed using t-test (for continuous variables, e.g. difference in change in ARMS

scores or MUSE scores) or chi-square test (for categorical variables, e.g. difference in change in % with complete PML understanding or % with complete adherence as per EMP). In Pilot Trial B, significant difference, at 2 weeks post-randomization, in the 3 medication-related outcomes between the 2 arms will be assessed using t-test (for continuous variables, e.g. difference in the ARMS scores or MUSE scores) or chi-square test (for categorical variables, e.g. difference in % with complete PML understanding or % with complete adherence as per EMP). For agreement between medication adherence assessed using EMP and that assessed using the 3 other approaches, Bland-Altman plots[42] (adherence considered as continuous) and Cohen's kappa[43-45] (κ; adherence considered as categorical) will be used. While our findings will only provide a general sense of the intervention impact, they will primarily inform which measures to use for the subsequent RCT and for determining its optimal sample size. We will also tabulate participation rates and loss to follow-up.

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator(s)/institution(s) will permit study-related monitoring, audits and/or IRB review and regulatory inspection(s), providing direct access to source data/document.

10. QUALITY CONTROL AND QUALITY ASSURANCE

The research assistant engaged will be responsible for administering the study protocol. A clearly drafted protocol will be provided to the research assistant prior to initiation of the study, with members of the study team available throughout the study period for the research assistant to clarify at any point if unclear. Members of the study team from SGH Pharmacy Department, overseen by the Principal Investigator, will also be working closely with the research assistant throughout the study period at SGH DMC.

11. ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practice and the applicable regulatory requirements.

This final Study Protocol, including the final version of the Participant Information and Consent Form, must be approved in writing by the Centralised Institutional Review Board (CIRB), prior to enrolment of any patient into the study.

The principal investigator is responsible for informing the CIRB of any amendments to the protocol or other study-related documents, as per local requirement.

11.1. Informed Consent

The consent process with the potential participant will take place at the outpatient clinic at SGH DMC level 3, which is a quiet and conducive environment that is usually familiar to patients. Otherwise, a separate room can be provided for potential participants who prefer a more private setting. Consent will be taken by the research assistant, who will provide necessary information in

accordance to the drafted Participant Information Sheet and Consent Form. As this study is likely to recruit a majority of non-English speakers, the Participant Information Sheet and Consent Form will be prepared in the 4 official languages (English, Mandarin, Malay and Tamil).

The research assistant will provide potential participants with ample time to consider and consult their family members as necessary, and reinforce that they are free to refuse participation, which will in no way affect the medications they receive from the pharmacy usually.

11.2. Confidentiality of Data and Patient Records

All research data will be soft copy and stored on password-protected PC/laptops. Only the study team (principal investigator, co-investigators and research assistants) will have access to the research data, which will be password protected. All soft copy research data will be coded, with participants' identifiers stored separately from research data, and only available on computers within the institution.

12. PUBLICATIONS

The purpose of the 2 pilot trials conducted in this study is to gain experience and collect data to allow selection of an optimal trial design, and refine protocols for recruitment, engagement and retention of study participants for a larger RCT in future, as well as determine variability in outcomes so that the larger RCT is appropriately powered to detect meaningful differences in the outcomes. Should any findings from this study be published, source of funding of this study (as stated in section 14) will be acknowledged, together with any subsequent assistance that is received for the study from individuals not part of the study team.

13. RETENTION OF STUDY DOCUMENTS

After study completion, research data will be stored on institution computers and remain password-protected, for a minimum of 7 years after completion of research study or date of publication of the research using the research data, whichever is later.

14. FUNDING and INSURANCE

This study will be funded by the Population-based, Unified, Learning System for Enhanced and Sustainable Health Centre Grant (PULSES CG).

List of Attachments

Appendix 1 References

Appendix 1

1. Malhotra R, Bautista MAC, Muller AM, et al. The Aging of a Young Nation: Population Aging in Singapore. *Gerontologist* 2019; 59: 401-410. 2018/12/06. DOI: 10.1093/geront/gny160.
2. Qato DM, Alexander GC, Conti RM, et al. Use of Prescription and Over-the-counter Medications and Dietary Supplements Among Older Adults in the United States. Jama 2008; 300: 2867-2878. 2008/12/26. DOI: 10.1001/jama.2008.892.
3. Pasina L, Brucato AL, Falcone C, et al. Medication Non-Adherence Among Elderly Patients Newly Discharged and Receiving Polypharmacy. *Drugs & Aging* 2014; 31: 283-289. 2014/03/08. DOI: 10.1007/s40266-014-0163-7.
4. The Statutes of the Republic of Singapore. The Medicines Act of Singapore (Revised Edition), Available at https://sso.agc.gov.sg/Act/MA1975 (1985, accessed 13 June 2018).
5. Shrank WH, Gleason PP, Canning C, et al. Can improved prescription medication labeling influence adherence to chronic medications? An evaluation of the Target pharmacy label. *J Gen Intern Med* 2009; 24: 570-578. 2009/02/28. DOI: 10.1007/s11606-009-0924-x.
6. Dowse R and Ehlers M. Medicine labels incorporating pictograms: do they influence understanding and adherence? *Patient education and counseling* 2005; 58: 63-70. 2005/06/14. DOI: 10.1016/j.pec.2004.06.012.
7. Martin D, Kripalani S and Durapau VJ, Jr. Improving medication management among at-risk older adults. *J Gerontol Nurs* 2012; 38: 24-34; quiz 36-27. 2012/05/17. DOI: 10.3928/00989134-20120509-01.
8. Davis TC, Wolf MS, Bass PF, 3rd, et al. Low literacy impairs comprehension of prescription drug warning labels. *J Gen Intern Med* 2006; 21: 847-851. 2006/08/03. DOI: 10.1111/j.1525-1497.2006.00529.x.
9. Shrank W, Avorn J, Rolon C, et al. Effect of content and format of prescription drug labels on readability, understanding, and medication use: a systematic review. *Ann Pharmacother* 2007; 41: 783-801. 2007/04/12. DOI: 10.1345/aph.1H582.
10. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *Jama* 2003; 289: 1107-1116. 2003/03/08. DOI: 10.1001/jama.289.9.1107.
11. Bosworth HB, Granger BB, Mendys P, et al. Medication adherence: a call for action. *Am Heart J* 2011; 162: 412-424. 2011/09/03. DOI: 10.1016/j.ahj.2011.06.007.
12. Malhotra R, Bautista MAC, Tan NC, et al. Bilingual Text With or Without Pictograms Improves Elderly Singaporeans' Understanding of Prescription Medication Labels. *Gerontologist* 2019; 59: 378-390. 2017/12/01. DOI: 10.1093/geront/gnx169.
13. Statistics Do. General household survey 2015. Department of Statistics, Ministry of Trade and Industry, Singapore Singapore, 2015.
14. Malhotra R, Bautista MAC, Tan NC, et al. Bilingual Text With or Without Pictograms Improves Elderly Singaporeans' Understanding of Prescription Medication Labels. The Gerontologist 2019; 59: 378-390. DOI: 10.1093/geront/gnx169.
15. Gerrig R and Zimbardo P. Psychology and Life 16 Ed. Boston, MA. Allyn and Bacon. Pearson Education, 2002.
16. Law AV and Zargarzadeh AH. How do patients read, understand and use prescription labels? An exploratory study examining patient and pharmacist perspectives. International Journal of Pharmacy Practice 2010; 18: 282-289.
17. Dennison CR, McEntee ML, Samuel L, et al. Adequate health literacy is associated with higher heart failure knowledge and self care confidence in hospitalized patients. The Journal of cardiovascular nursing 2011; 26: 359.
18. Macabasco-O'Connell A, DeWalt DA, Broucksou KA, et al. Relationship between literacy, knowledge, self-care behaviors, and heart failure-related quality of life among patients with heart failure. Journal of general internal medicine 2011; 26: 979-986.
19. Tomaszewski D, Aronson BD, Kading M, et al. Relationship between self-efficacy and patient knowledge on adherence to oral contraceptives using the Morisky Medication Adherence Scale (MMAS-8). Reproductive health 2017; 14: 110.
20. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. Psychological review 1977; 84: 191.
21. Ogedegbe G, Mancuso CA, Allegrante JP, et al. Development and evaluation of a medication adherence self-efficacy scale in hypertensive African-American patients. Journal of clinical epidemiology 2003; 56: 520-529.
22. Nafradi L, Nakamoto K and Schulz PJ. Is patient empowerment the key to promote adherence? A systematic review of the relationship between self-efficacy, health locus of control and medication adherence. PLoS One 2017; 12: e0186458. 2017/10/19. DOI: 10.1371/journal.pone.0186458.

23. Bandura A. Health promotion by social cognitive means. Health education & behavior 2004; 31: 143-164.
24. Reisi M, Mostafavi F, Javadzade H, et al. Impact of health literacy, self-efficacy, and outcome expectations on adherence to self-care behaviors in Iranians with type 2 diabetes. Oman medical journal 2016; 31: 52.
25. Lorig KR and Holman HR. Self-management education: history, definition, outcomes, and mechanisms. Annals of behavioral medicine 2003; 26: 1-7.
26. World Health Organization. Adherence to Long-term Therapies: Evidence for action, http://www.who.int/chp/knowledge/publications/adherence_report/en/ (2003, accessed 13 June 2018).
27. Loon SC, Jin J and Jin Goh M. The relationship between quality of life and adherence to medication in glaucoma patients in Singapore. J Glaucoma 2015; 24: e36-42. 2013/11/20. DOI: 10.1097/IJG.0000000000000007.
28. Heng JK, Koh LJ, Toh MP, et al. A study of treatment adherence and quality of life among adults with chronic urticaria in Singapore. Asia Pac Allergy 2015; 5: 197-202. 2015/11/06. DOI: 10.5415/apallergy.2015.5.4.197.
29. Yap AF, Thirumoorthy T and Kwan YH. Systematic review of the barriers affecting medication adherence in older adults. Geriatr Gerontol Int 2016; 16: 1093-1101. 2016/10/21. DOI: 10.1111/ggi.12616.
30. Mullen RJ, Duhig J, Russell A, et al. Best-practices for the design and development of prescription medication information: A systematic review. Patient education and counseling 2018; 101: 1351-1367. 2018/03/20. DOI: 10.1016/j.pec.2018.03.012.
31. Kripalani, S., Risser, J., Gatti, M. E., & Jacobson, T. A. (2009). Development and Evaluation of the Adherence to Refills and Medications Scale (ARMS) among Low-Literacy Patients with Chronic Disease. Value in Health, 12(1), 118–123. https://doi.org/10.1111/j.1524-4733.2008.00400.x.
32. Chen, Y. J., Chang, J., & Yang, S. Y. (2020). Psychometric Evaluation of Chinese Version of Adherence to Refills and Medications Scale (ARMS) and Blood-Pressure Control Among Elderly with Hypertension. Patient Preference and Adherence, Volume 14, 213–220. https://doi.org/10.2147/ppa.s236268
33. Raehl CL, Bond CA, Woods T, et al. Individualized drug use assessment in the elderly. Pharmacotherapy 2002; 22: 1239-1248. 2002/10/23. DOI: 10.1592/phco.22.15.1239.33473
34. Stirratt MJ, Dunbar-Jacob J, Crane HM, et al. Self-report measures of medication adherence behavior: recommendations on optimal use. Transl Behav Med 2015; 5: 470-482. 2015/12/02. DOI: 10.1007/s13142-015-0315-2.
35. Lam WY and Fresco P. Medication Adherence Measures: An Overview. Biomed Res Int 2015; 2015: 217047. 2015/11/06. DOI: 10.1155/2015/217047.
36. Checchi KD, Huybrechts KF, Avorn J, et al. Electronic medication packaging devices and medication adherence: a systematic review. Jama 2014; 312: 1237-1247. 2014/09/24. DOI: 10.1001/jama.2014.10059.
37. The Statutes of the Republic of Singapore. Health Products Act (CHAPTER 122D), Health Products (Therapeutic Products) Regulations 2016 Available at https://sso.agc.gov.sg/SL/HPA2007-S329-2016?DocDate=20190215#pr17- (2016, accessed 12 December 2019).
38. Choo F. Making medication labels easier for seniors to understand https://www.straitstimes.com/singapore/health/making-medication-labels-easier-for-seniors-to-understand.(2019, accessed 12 December 2019).)
39. Singapore MoH. Pharmaceutical Care Services Guidelines 2019.
40. Grymonpre RE, Didur CD, Montgomery PR, et al. Pill count, self-report, and pharmacy claims data to measure medication adherence in the elderly. Annals of Pharmacotherapy 1998; 32: 749-754.
41. Cameron KA, Ross EL, Clayman ML, et al. Measuring patients' self-efficacy in understanding and using prescription medication. *Patient education and counseling* 2010; 80: 372-376. 2010/07/24. DOI: 10.1016/j.pec.2010.06.029.
42. Hanneman SK. Design, analysis, and interpretation of method-comparison studies. AACN Adv Crit Care 2008; 19: 223-234. 2008/06/19. DOI: 10.1097/01.AACN.0000318125.41512.a3.
43. Cohen J. A coefficient of agreement for nominal scales. Educational and psychological measurement 1960; 20: 37-46.
44. Sim J and Wright CC. The kappa statistic in reliability studies: use, interpretation, and sample size requirements. Physical therapy 2005; 85: 257-268.
45. Landis JR and Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977; 33: 159-174. 1977/03/01.