STUDY PROTOCOL

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The Impact of Collaborative Care Model in the Management of Primary Care Patients with Type 2 Diabetes Mellitus in Singapore

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Background and Rationale:
In Singapore, the prevalence of diabetes mellitus (DM) was approximately 12.8% in 2014[1] and the prevalence was projected to rise to 22.7% in 2035.[2] In 2015, the International Diabetes Federation (IDF) reported that Singapore has the second highest proportion of diabetic patients among developed nations.[1] In 2010, the total economic cost for working-age diabetic patients in Singapore was USD 787 million, and it was projected to rise to USD 1867 million in 2050.[3] The incidence of DM increases with age, and this is of particular concern because Singapore is one of Asia's fastest aging populations.[4,5] As such, DM is becoming an increasingly important health issue that needs to be addressed with urgency.

Uncontrolled DM is associated with significant microvascular complications such as retinopathy, nephropathy and neuropathy; it can also result in macrovascular complications such as stroke and myocardial infarction.[6] DM is considered a coronary heart disease risk equivalent, and its contribution to cardiovascular diseases (CVD) increases patient morbidity and mortality by as much as 60% in Singapore.[7,8] Studies have shown that the prognosis for subjects with DM without prior CVD was worse than that for non-diabetic subjects with prior CVD.[9,10] Therefore, in order to prevent and reduce the occurrence of short-term and long-term macrovascular and microvascular complications, a holistic management of DM should include close monitoring of patient's blood pressure (BP) and lipid profile in addition to good glycaemic control.

The management of DM and its associated co-morbidities can be complex, and often requires multiple medications along with strict lifestyle modifications.[11,12] Since chronic diseases are life-long and without cure, strict and continuous lifestyle modifications can be exhausting; and for most patients, pharmacotherapy becomes the mainstay of chronic disease management. However, with time, pill burden may increase, and medication adherence and drug interactions can become a problem for many patients with chronic diseases.[13,14] In addition, limited physician-patient contact can result in suboptimal care as different aspects of DM care such as extraction of subjective data from a thorough interview with the patients, monitoring of objective data trends, drug optimization, medication tolerability, lifestyle modifications and accuracy in the use of medications and auxiliary devices cannot be addressed.[13,15] Such situations may give rise to not only therapeutic failure but also potential drug-related adverse events or drug-drug interactions, which can increase the risk of drug-related mortality and morbidity.[11]

Studies conducted in different countries have shown that due to the complex nature of the chronic disease state, a collaborative care model can be a more effective approach in managing patients with DM.[11,14-16] In addition to physicians, such a collaborative effort often includes clinical pharmacists, nurses, dietitians and/or social workers. Care carried out by these experts in different aspects of DM has been found to yield positive treatment outcomes for patients.[13,16,17]

In countries such as Singapore, Jordan, the United States, and Canada, the collaborative care model has been shown to optimize therapeutic outcomes of patients with DM as evidenced by improvements in surrogate markers such as HbA1c, BP, LDL and TG (Table 1).[18-21] These studies had a follow-up period ranging from 3 to 9 months. Although the degree or level of improvements vary across countries, the collaborative care model has shown to improve clinical outcomes of patients with DM.

Table 1. Improvements in Surrogate Markers from Collaborative Care Model

Author (year)	Study Design	Country	Clinical Outcomes				Comments
			HbA1c (%)	SBP (mm Hg)	LDL (mmol/L)	TG (mmol/L)	
Siaw MYL et al. (2017)[18]	Randomised controlled trial	Singapore	INT: -0.3% at 3-month and -0.5% at 6-month	No significant changes over 6 months	No significant changes over 6 months	No significant changes over 6 months	Treatment satisfaction and distress were also assessed (better outcome in INT). INT also shown to significantly reduce direct medical costs as compared to UC.
Jarab AS et al. (2012)[19]	Randomized controlled trial	Jordan	INT: -0.8; UC: +0.1	INT: -5.8; UC: +1.1	INT: -0.6; UC: No change	INT: -0.5; UC: +0.2	Medication adherence and self-care techniques also improved in INT.
Scott DM et al. (206)[20]	Randomised controlled trial	United States of America	INT: -1.7; UC: -0.9	INT: -3.4; UC: +2.1	INT: -0.5; UC: -0.2	NIL	Quality of life was assessed using DQOL; some components favour INT but total scores were not significantly different between INT and UC.
Katherine IT et al. (2005)[21]	Randomised controlled trial	Canada	INT: -0.29; UC: +0.72	INT: -2.0; UC: +7.0	INT: -7.7; UC: +1.6	INT: +40.6; UC: -0.9	DQLCLTQ and SF-36 were assessed. DQLCLTQ domains such as global role functioning, diabetes impact, health distress, and social stigma were significantly improved in INT.

Abbreviations: INT, intervention; UC, usual care.

In addition, positive humanistic outcomes were also illustrated in studies that looked at the effectiveness of collaborative care in terms of patient quality of life and medication adherence. In one study, it was shown that there was a statistically significant increase in mean ± standard deviation WB-Q12 scores (well-being) in the intervention group (21.9 ± 6.8 to 23.4 ± 6.8, p=0.04) but no change among controls at follow-up.[13] Furthermore, the total mean ± SD BMQ score (beliefs about medications and medication adherence) dropped from 3.89 ± 1.78 to 2.74 ± 1.39 in the intervention group and increased from 2.81 ± 1.15 to 3.90 ± 1.45 (p<.001) for the control group.[13]

Lastly, a collaborative care approach has demonstrated a reduction in overall health care costs for patients with DM.[22] One study found that collaborative care was associated with a 62% decrease in the annual cost of treatment ($107,939.99 vs. $41,106.30 [U.S.]).[22] Furthermore, after accounting for the additional cost of glucose monitoring ($30,604), there was still 34% annual savings for patients.[22]

Currently in Singapore, the effectiveness of the collaborative care model has only been evaluated prospectively for a duration of 6 months. The long-term impact of this care approach on the clinical, humanistic and economic outcomes have yet to be elucidated.

In summary, due to the complex nature and multifactorial causes of chronic diseases, healthcare systems around the globe face many challenges as they work to deliver effective chronic disease management. Evidence has shown that health care can be delivered more effectively and efficiently through a multidisciplinary team approach, in which providers are supported by experts from different disciplines, and as a result are better equipped with the necessary resources and knowledge to manage their patients' chronic diseases.[18-21] With a diverse group of healthcare professionals on board, the healthcare team can ensure that their patients' treatment goals are attained in the short-term and maintained in the long-term.

Specific Aims and Objectives

The purpose of this study is to determine the effectiveness of the collaborative care model in Singapore in which clinical pharmacists, nurses and dietitians are active participants who collaborate with physicians in caring for patients with type 2 DM. Since type 2 DM is a cardiovascular risk equivalent, co-morbidities such as hypertension (HTN) and dyslipidaemia (DLP) will also be evaluated to assess the holistic care provided for our patients afflicted with these top chronic diseases in Singapore.

Specifically, this study aims to evaluate the long-term effectiveness and sustainability of an integrated collaborative care model comprising of a healthcare team (physician, clinical pharmacist, nurse, and/or dietitian) compared to the usual or conventional healthcare model (physician-centred care) mainly in the following outcomes (Table 2).

Table 2. Outcome Measures for Proposed Study

Types of Outcomes	Descriptions
Clinical	• Glycated haemoglobin (HbA1c), systolic blood pressure (SBP), low density lipoprotein (LDL), total cholesterol, high density lipoprotein (HDL) and fasting triglyceride (TG) levels • Incidence of minor and major hypoglycaemia • DM-related clinical visit and hospitalization
Humanistic	• Health-related quality of life • Self-care management • Diabetes-related distress
Economic	• Cost effectiveness • Productivity

The central hypothesis of this study is that patients with type 2 DM under the collaborative care model will have greater improvements in the clinical, humanistic and economic outcomes assessed than those under conventional care.

Data collection period:

12 March 2018 to 12 March 2020

Study Design and Methodology:

Study Design and Setting

This proposed project is a prospective, randomized controlled study to be conducted over a 12-month period. This multi-centre study will be conducted in Bukit Batok and Choa Chu Kang Polyclinics.

Study Participants

Patients aged ≥ 21 years with Type 2 DM (HbA1c > 7%) and polypharmacy (≥ 5 medications) will be eligible for this study. Patients with Type 1 DM or who are unable to communicate independently in English, Chinese or Malay will be excluded from this study.

Procedures

Eligible patients will be screened and identified by research assistants of this study. Upon agreeing to participate in the study and signing of the informed consent, the patients will be randomised to either the control or intervention group using a random number generator or an equivalent by the research assistants.

Patients randomly assigned to the usual or conventional care arm may be subject to as needed referral to the nurses for soft skill-related DM counselling and dietitian for diet control, at the discretion of the physician. These patients may be seen by different physicians at each visit, and pharmacists will not be involved in drug optimization except for dispensing.

Patients randomly assigned to the collaborative care arm will see a healthcare team comprising clinical pharmacists in addition to physicians, nurses and dietitians. The clinical interventions carried out by the clinical pharmacist include but are not limited to counselling patients about drug therapy, performing simple physical assessments, ordering pertinent follow-up visits and laboratory tests on behalf of the physicians, and initiating, titrating, and terminating medications per the NHG Hypertension, Diabetes, Lipids Clinic (HDL-C) Protocol and under the supervision of the physicians as appropriate. The supervision is usually in the endorsement of prescriptions prepared by clinical pharmacists. In addition, the clinical pharmacist will serve as a bridge between patients and physicians to increase communication, and patients will need to be seen by physicians at least every four months. As needed, referrals to nurses and dieticians will also be actively made by the clinical pharmacist and vice versa. The clinical pharmacist will schedule clinic appointments approximately every four to six weeks in the 12-month interventional period. If the patient's DM is well-controlled, i.e. with stable improvements in clinical measures, the clinical pharmacist may replace one or two clinic visits with telephone counselling at his/her discretion. All clinical pharmacists are board-certified pharmacotherapy specialists and/or board-certified ambulatory care pharmacist, and they have undergone the 3-month internal rotational endocrinology training held at Tan Tock Seng Hospital, comprising preceptors who are endocrinologists, senior clinical pharmacists, diabetes nurse educators, dietitian, and podiatrist, similar to the previous study conducted.[18]

Data Collection:
The types of outcome measures and period of assessment are summarized in Table 3 below. Patient demographics, past medical history, and current medication use for both control and intervention group will be collected at enrolment. Serum creatinine level will also be followed up at every 6-month period to ensure that any diabetic complications are not due to change in organ function over time.

Table 3. Summary of Outcome Measures

Outcomes	**Parameters**	**Time Period**		
1. Clinical outcomes	**Treatment goal**	**Baseline***	**6-month**	**12-month**
1.1 HbA1c	≤ 7%	√	√	√
1.2 SBP	< 130 mm Hg	√	√	√
1.3 LDL	< 2.6 mmol/L	√	√	√
1.4 HDL	≥ 1.0 mmol/L	√	√	√
1.5 Total cholesterol	< 5.2 mmol/L	√	√	√
1.6 TG	< 2.3 mmol/L	√	√	√
1.7 Self-reported incidence of minor and major hypoglycaemia	N/A	√	√	√
1.8 DM-related clinic visit and hospitalization	N/A	-	√	√
2. Humanistic outcomes	**Measurement instrument**	**Baseline***	**6-month**	**12-month**
2.1 Health-related quality of life	EQ-5D-5L, ADDQoL[23]	√	√	√
2.2 Self-care management	SDSCA[24]	√	√	√
2.3 Diabetes-related distress	PAID[25]	√	√	√
3. Economic outcomes	**Type of costs**	**Baseline***	**6-month**	**12-month**
3.1 Costs	Direct costs	-	√	√
3.2 Productivity	Indirect costs (WPAI-GH)	-	√	√

√: to be measured
*Baseline refers to any time within the past 6 months prior to recruitment
Abbreviations: HbA1c, glycated haemoglobin; SBP, systolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; DM, diabetes mellitus; EQ-5D-5L, EuroQoL 5-dimension 5-level; ADDQoL, Audit of Diabetes-Dependent Quality of Life; SDSCA, Summary of Self Care Activities; PAID, Problem Areas in Diabetes; WPAI-GH, Work Productivity Activity Impairment-Global Health.

Clinical Outcomes
The main clinical parameters to be collected include HbA1c, SBP, total cholesterol, LDL, HDL, and TG. These short-term surrogate markers are predictive of the development of long-term DM-related complications. In addition, total cholesterol and other lipid parameters allow for estimation of cardiovascular risk. While several laboratory measures of glycemic levels are available, HbA1c will be used in this study as it is a recommended and reliable index of mean glycemic control over three months. Other outcome measures include: 1) incidence of minor and major hypoglycemia reported by patients, 2) frequency of DM-related clinic visits (by physician, pharmacist, nurses, dietitians) as indicated on patients' appointment card and hospitalizations. Minor hypoglycemic events are defined as blood glucose of < 4.0 mmol/L or signs and symptoms with known precipitating causes such as irregular eating habits, increased daily activity or other attributes that can be modified. The minor hypoglycemic event should allow the patient to recover quickly with or without the ingestion of fast-acting glucose. Major hypoglycemic events are defined as any hypoglycemic symptoms, regardless of frequency, which require help from another person. The clinical information and laboratory values will be collected from the clinical databases available at the study sites, patient case notes, and patient self-reported questionnaires at baseline, at 6- and 12-month during the study period. Baseline

laboratory values will be collected at enrolment. If values are not available at enrolment, the most recent value available within the 6 months preceding enrolment will be recorded.

Humanistic Outcomes
Health-related quality of life (HRQoL) will be assessed using Research Assistant-administered questionnaires at baseline and as close to the 6-month and 12-month follow-ups as possible. The HRQoL measures will include a generic measure, EQ-5D-5L, and a DM-specific measure, the Audit of Diabetes Dependent Quality of Life (ADDQoL), and Problem Areas in Diabetes (PAID). Self-care management capabilities of patients will be assessed by the Summary of Diabetes Self-Care Activities Measure (SDSCA).

Economic Outcomes
The economic evaluation will be conducted from an institutional perspective. Direct healthcare costs will be estimated over 12 months. The direct costs will include physicians' consultation fees, laboratory and procedures, medication costs, DM-related hospitalization, and DM-related A&E visits.

Number of Subjects to be enrolled:
A 12-month study conducted in the United States of America involving the collaborative care model reported an effect size of 0.4.[20] With an allocation ratio of 1:1 into the intervention or control arms, approximately 125 patients are needed in each arm, to obtain a statistical power of 80% (two-sided Type I error rate = 0.05) and after taking into account a 20% dropout rate. As such, 250 patients will be needed to assess the effectiveness of a collaborative care model versus the usual model of care in the polyclinics.

Data source:
Clinical data will be collected from patient electronic case notes, prescription records accessed from CPSS2 and iPharm and investigation results from the electronic laboratory module in CPSS2. Humanistic data and incidence of hypoglycaemia will be elucidated through participant's self-reported questionnaires. Cost data will be obtained from the respective institution financial databases.

Data Analysis:
Descriptive analyses will be performed on all variables. The differences in the improvement of clinical and patient-reported outcomes will be examined between the two groups using the Student's t test or Wilcoxon rank-sum test as appropriate. Categorical data between the two study groups will be analyzed using the Chi-square test for independence or Fisher's exact test when expected cell size is less than 5. Pearson's product-moment correlation will be used to examine correlations between continuous variables such as HbA1c and HRQoL scores. Baseline factors that are significant in the bivariate analysis will be included in a multiple linear regression model to investigate the unique impact of the intervention on and the unique association of individual factors with each outcome score while adjusting for other covariates. The level of Type I error rate will be set at $P < 0.05$.

The sum of the costs incurred will be compared between the two groups using the Wilcoxon rank-sum test as the cost data are not expected to be normally distributed. General linear models with a log-link to the gamma distribution will be used to conduct multivariate analysis of costs between the groups. Gamma distributions are well suited for cost data since it a right-

skewed distribution. A cost-effectiveness analysis will be performed in which the effectiveness is defined by reduction in HbA1c between baseline and the 12-month follow-up. The incremental cost-effectiveness ratio will be calculated in which the difference in total costs between two groups is divided by the difference in the reduction in HbA1c between the two groups. Sensitivity analysis will be conducted to evaluate the influence of uncertainties in the variables and assumptions employed on the analysis results.

Data Entry and Storage:
All research-related electronic data collected will be de-identified, coded and entered in Microsoft Excel spreadsheet that will be password-protected and will be stored together with research-related paper documents in the investigators office at the National University of Singapore Department of Pharmacy, Faculty of Science. All patient information will be kept strictly confidential, following the policies of the study institution(s) involved. For hardcopy data, they will be stored in designated locked cabinet(s) or room(s) that are accessible to authorized study personnel only. For electronic data, they will be stored on in a secured computer that is password-protected. The databases will not contain subject identifiers and the data linking subject identifiers and the subject identification codes will be stored separately. These documents will be retained for a minimum of three years after study completion or as per institutional policies.

Confidentiality of Data and patient Records:
Investigators in this study will have access to all research-related data on a need-to-know basis or as per institutional policies. Collaborators in this study will only have access to research-related data that has been coded and has no patient related identifier. Only the principal investigators and co-investigators or collaborators will have access to the data in the excel spreadsheet. There will not be any sharing or releasing of raw data to any other persons.

Publication:
The principal investigators and co-investigators/collaborators are entitled to full de-identified data access and to publish the study findings as appropriate.

Patients Reimbursement:
Upon completion of the baseline questionnaires, the participant will be given a glucometer and a maximum of 4 bottles (each bottle with 50 units) of test strips and lancets. If the participant completes the questionnaires at the 6-month time point, he / she will be reimbursed with $20.00 in cash or equivalent. If the participant completes the questionnaires at the 12-month time-point, he / she will be reimbursed with $30.00 in cash or equivalent.

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