PROPOSED RESEARCH PROJECT

a) **Title:**

10-year Risk Prediction Models of Complications and Mortality of Diabetes Mellitus in Chinese Patients in Primary Care in Hong Kong

b) **Introduction:**

Diabetes Mellitus (DM) is a well-recognized public health issue, affecting 415 million people and costing HK$5.2 trillion in global health expenditures worldwide (1). It is estimated 568,000 people are living with DM in Hong Kong, and the projected number will increase to 781,000 in 2040 (1). In Hong Kong, the health care costs for diabetic patients are estimated to be HK$2 billion accounting for 4.5% of the gross domestic product (GDP) per capita, and a major health service burden accounting for 200,000 (17% of total) hospital admissions with 1.2 million hospitalization days per year (1, 2).

DM can lead to many complications resulting in morbidity and mortality. According to the International Diabetes Federation (IDF), in 2015, diabetes led to 5.0 million (14.5% of all deaths) deaths worldwide which translated to one death every six seconds and approximately 70% of DM related deaths were attributed to cardiovascular diseases (CVD) (1). The development of diabetes-related complications significantly increases medical costs (1). A previous local study also found that the direct medical cost for diabetic patients with CVD were 1.1 times more than patients without CVD in Hong Kong (3).

To prevent DM complications, the American Heart Association (AHA) guidelines recommend primary care providers to provide regular assessment and management of risk factors for patients especially those who are at high risk of developing DM complications. Although the National Cholesterol Education Programme (NCEP) in the United States has suggested that all diabetic patients be treated as if they had CHD, however the observed rate of cardiovascular diseases (CVD) vary vastly among different diabetic patients (4). The American Diabetes Association (ADA) and the Canadian Diabetes Association guidelines both include 10-year overall CVD risk stratification into account to identify high-risk patients for more intensive medical and psychosocial interventions (5). The guidance of stain prescription from the American College of Cardiology and the American Heart Association, which is consistent with

the ADA, also takes predicted 10-year overall CVD risk into account (6). The ADA recommends aspirin treatment for diabetic patients with a 10-year predicted over CVD risk higher than 10% (5). Studies in the United States, the United Kingdom, Australia, New Zealand and Hong Kong showed that systematic risk assessment and risk-stratified management initiatives in primary care settings could improve clinical outcomes such as Haemoglobin A1c (HbA1c), blood pressure (BP) and low-density lipoprotein cholesterol (LDL-C), as well as reduce utilization of health services including Accident and Emergency (A&E) attendance, and hospital admissions (7). In 2009, the Hong Kong Hospital Authority (HA) made an initiation to enhance the quality of DM care in all HA primary care clinics by the introduction of the Multi-disciplinary Risk Assessment and Management Programme – Diabetes Mellitus (RAMP-DM) to systematically assess the CVD risk of DM patients and then managed according to risk-stratified protocols (8).

A key to cost-effective management of DM is an accurate risk assessment and stratification system that identifies high-risk patients for more intensive medical and psychosocial interventions. At the same time, an accurate estimation of risk distribution can inform policy-makers to allocate appropriate resources and plan services that can maximum population health benefit for DM patients. Existing prediction functions commonly used include the Framingham [10-year] (9, 10), the United Kingdom Prospective Diabetes Study (UKPDS) [5-year] (11, 12) and the local (Joint Asia Diabetes Evaluation (JADE) [5-year] (13, 14) models. However, our earlier study on 10,969 diabetic patients managed in the HA primary care clinics showed none of these models was accurate in predicting the observed events over a 4-year follow up for this patient population (15). The Framingham models overestimated the risks of CHD and stroke by 2.0 times and 23%, respectively(15). Several other studies have also concluded that the Framingham models were not applicable to Chinese populations (16). The UKPDS risk prediction models also showed a tendency to overestimate the risk of CHD and stroke by 5.1 times and 51%, respectively (15). The JADE prediction models, although developed from the local Chinese population, overestimated the 4-year CHD, stroke rates by 2.9 times and 41%, respectively, when compared to the actual 4-year observed incidences (15). The JADE prediction models were developed from data of Chinese diabetic patients under specialist care who are more likely have more severe disease and many had complications such as stroke or CHD at baseline (13, 14), which may explain why they tend to over predict complications in primary care DM patients. The

cohort from JADE was collected almost 20 years ago (1995) and the number of subjects (around 7000) was relatively small, which may not be generalizable to the 400,000 DM patients under HA care. Furthermore, JADE only provides 5-year risk prediction although 10-year risk is the international standard (17).

We have also identified some deficiencies in existing risk prediction models that might have affected their accuracy. Firstly, gender is a factor that is of concern in the analyses of risk factors and CVD/mortality because males are typically associated with a higher risk of CVD/mortality (18), but statistical adjustment for gender is often insufficient to control for varying risk-factor profiles and CVD/mortality incidence (19). Secondly, there are possible interaction effects between age and risk factors on the CVD/mortality as the magnitude of the effect of specific risk factors such as LDL-C on the CVD/mortality may decrease with age (20). Thus, the interaction term between age and risk factors should be considered when developing the risk prediction models. Thirdly, many studies including our study and post-hoc analysis of JADE illustrated that there were curvilinear association (J or U shape) between HbA1c/ SBP/ DBP/ LDL-C/ BMI and the risk of CVD/mortality (21, 22), and thus the quadratic term of such clinical parameters should be evaluated when developing the risk prediction models. Finally, current risk prediction models were based on a single measurement (i.e. baseline) of clinical parameters such as HbA1c, SBP, DBP and BMI, but the use of repeated measures, e.g. average of all available readings or last available before event, may be more better predictors. The studies from JADE also suggest the inclusion of factors such as drug treatments and subsequent HbA1c and BP may improve the predictive power of the models (13, 14).

Inaccurate risk stratification may lead to inappropriate risk-stratified interventions. There is a need for new robust risk prediction models for the prediction of 10-year CVD risk and mortality for primary care Chinese patients to enable accurate risk stratification of DM patients in the HA on-going RAMP-DM or other primary care systematic risk-stratified multi-disciplinary management programmes. Furthermore,

robust risk prediction models for the overall prediction of first CVD and all-cause mortality can inform policy makers in service planning and resource allocation.

c) **Aims, Objectives and** Hypotheses

This study aims to develop 10-year risk prediction models for total CVD and all-cause mortality among Chinese diabetic patients in primary care. Risk prediction models for individual DM complications including CHD, heart failure, stroke and ESRD will also be developed.

The objectives are to:

1. Calculate the 10 years incidence of total CVD, all-cause mortality and each major DM complication in Chinese DM patients in primary care.
2. Determine the risk factors that significantly predict total CVD, all-cause mortality and each major DM complication for Chinese DM patients in primary care.
3. Develop and validate risk prediction models for total CVD, all-cause mortality and each major DM complication for Chinese DM patients in primary care.
4. Develop a risk prediction nomogram and chart for the risk of total CVD, all-cause mortality for Chinese DM patients in primary care

Hypotheses

The following hypotheses will be tested:

1. Patient socio-demographic, clinical parameters, disease characteristics, and treatment modalities (these independent variables are described in the Methods section) are predictive of 10-year risk of total CVD, all-cause mortality and individual DM complication as a dependent variable.
2. The risk prediction models for total CVD, all-cause mortality and individual DM complication developed in this study can have over 70% of discriminating power.

d) **Plan of Investigation:**

(i) **<u>Study design</u>**

A 10-year retrospective study on a population-based cohort of Chinese DM patients in primary care.

(ii) **Subjects**

The cohort will include all patients with a documented clinical diagnosis of DM and were receiving care in the Hospital Authority (HA) primary care General Out-Patient Clinics (GOPC) and Family Medicine Clinics (FMC) on or before 1 July 2006 identified from the HA clinical management system (CMS) database.

Inclusion criteria

1. Age ≥ 18 years old
2. At least 1 GOPC/FMC attendance on or within 1 year before 1 July 2006
3. Had a CMS record of the coding of ICPC-2 of T89 (Diabetes insulin dependent) or T90 (Diabetes non-insulin dependent) on or before 1 July 2006

Exclusion criteria

1. Patients who had a diagnosis of any DM complications defined by the relevant ICPC-2 or ICD-9-CM (shown in the Method section) on or before 1 July 2006.
2. Patients exclusively managed by Specialist Out-Patient Clinic (SOPC) on or before 1 July 2006.

Sample size calculation

The detailed sample size calculation for each study outcome is attached in Appendix B. The required sample size is based on the requirements for the development and validation of the least common DM complication of ESRD. Specifically, based on our previous study, the 5-year incidence of ESRD was 1.9%(8), which can be extrapolated to a 10-year incidence of ESRD was 3.8% by assuming a constant incidence rate over time. To develop the risk prediction model for ESRD by multivariable Cox proportional hazard regressions with forward stepwise variables selection on 16 potential risks factors, we need 21,053 subjects using the 1 in 50 rule that 1 candidate predictor can be studied for every 50 events (23). To validate the risk prediction models, the area under the receiver operating characteristic curve (AUC) will be used to assess the discriminatory power of the predictive model on a separate sample of subjects. With 10 years incidence rate of ESRD was 3.8%(8), a total 14,307 subjects (544 subjects with ESRD and 13,763 subjects without ESRD) is needed to

ensure a precision of 0.05 for AUC of 0.7 by a 95% confidence interval.

Hence, a total 35,360 male and 35,360 female are needed for the development (training dataset) and validation of risk prediction models stratified by gender. The HA data set that we have obtained for our 5-year evaluation of quality of care and effectiveness of RAMP-DM study(8) has identified 120,857 DM patients under the care of public primary care on or before 1 Jan 2009, so we should be able to obtain sufficient number of subjects.

(iii) **Methods**

Each patient will be followed from 1 July 2006 to 31 December 2016 for the development of the indicator DM complications and mortality.

Definition of indicator DM complications

The incidence of four major DM complications (CHD, stroke, heart failure and ESRD), total CVD and all-cause mortality will be calculated. The incidence is counted from the earliest date of documented diagnosis defined by the relevant ICPC-2 and/ or ICD-9-CM coding recorded in the HA CMS database from 1 July 2006 to 31 December 2016. The relevant ICPC-2 and ICD-9-CM codes of each DM complication and mortality are determined by the academic and HA clinician co-investigators as listed below:-

1. CHD (ischaemic heart disease, myocardial infarction (MI), coronary death or sudden death) is defined by any of ICPC-2 K74 to K76 and ICD-9-CM 410.x, 411.x to 414.x, 798.x
2. Stoke (fatal and non-fatal stroke) is defined by any of ICPC-2 K89 to K91 or ICD-9-CM 430.x to 438.x.
3. Heart failure is defined by any of ICPC-2 K77 or ICD-9-CM 428.x
4. CVD is defined as the presence of any of CHD, heart failure and stroke ICPC-2 or ICD-9-CM codes listed in 1, 2 and 3 above.
5. ESRD is defined by any of ICD-9-CM 250.3x, 585.x, 586.x, or an eGFR<15mL/min/1.73m^2.
6. Mortality is identified from the Hong Kong Death Registry.

Risk factors to be Included in the Risk Prediction Models

Risk factors (independent variables) previously found to be associated with DM

complications from the literature (4) and those that are routinely available in primary care are selected to strike a balance between comprehensiveness and feasibility. The potential risk factors that will be explored include those related to patient's socio-demographics, clinical parameters, disease characteristics and treatment modalities. Patient socio-demographics include sex, age and smoking status. Clinical parameters include body mass index (BMI), haemoglobin A1c (HbA1c), systolic and diastolic blood pressure, lipid profile (total cholesterol, HDL-C, LDL-C, triglyceride), estimated glomerular filtration rate (eGFR) and albuminuria. Disease characteristics include the duration of DM and co-morbidity. Treatment modalities include the use of specific anti-hypertensive drugs, insulin, specific oral anti-diabetic drugs and lipid-lowering agents. The operational definitions of the risk factors are shown in appendix A. These factors, except sex, age, duration of DM and co-morbidity, are modifiable, which have implications for practice.

Data collection

In the middle of 2017, anonymous data from 1 January 2006 to 31 December 2016 of all DM patients who satisfy the inclusion criteria and without any exclusion criteria will be extracted by the HA statistics team from the HA clinical management system (CMS) database. We have successful experience in working with the HA in the extraction of similar data from 2009 to 2013 for our extended evaluation on quality of care and effectiveness of RAMP-DM study (7), and we have obtained preliminary agreement from the HA for the data extraction in the present study.

Outcome Measures

1. The incidence of total CVD, all-cause mortality and each of 4 major DM complications over 10 years
2. Factors predictive of total CVD, all-cause mortality and each of 4 major DM complications over 10 years
3. 10-year risk prediction models for total CVD, all-cause mortality and each of 4 major DM complications
4. Factors that have sufficient power to classify Chinese DM patients in primary care into risk group in terms of total CVD and all-cause mortality.

(iv) **Data processing and analysis**

The cohort will be stratified by gender. Descriptive statistics will be used to calculate the incidence of total CVD, all-cause mortality and each of 4 major DM complications will be analysed annually and cumulatively over 10 years with a 95% confidence interval. The distribution of risk factors will be cross-tabulated by complication or mortality events. The 10 year cumulative incidence of various DM complications and mortalities will be further analysed by Kaplan-Meier method. The Kaplan-Meier survival curve will be used to describe the survivorship of total CVD, all-cause mortality and each of 4 major DM complications in the study cohort over 10 years. Unadjusted associations between the risk factors and odds of events will be assessed by independent t-test for continuous variables or Chi-square test for categorical variables.

The cohort will be randomly split on a 2:1 basis, with the two-third sample used for developing the risk prediction models, and the other one-third sample used for validation of the risk prediction models. The analyses will be carried out separately for men and women.

Development of risk prediction models

Cox proportional hazard regressions with forward stepwise method will be used to develop the risk prediction models for total CVD, all-cause mortality and each of 4 major DM complications. If the main term of a clinical parameter is selected in the models, the quadratic term of such clinical parameter will be evaluated. Afterwards, the interaction terms between selected predictors and age will be also examined in the risk prediction models. Cox regressions is the most commonly used method in risk prediction models in the Framingham Heart Study (9, 10) and UKPDS (11, 12). It allows us to estimate the risk of disease or death for an individual, given their prognostic variables. A positive hazard ratio means a higher likelihood of event associated with that specific variable. Conversely, a negative hazard ratio means a lower likelihood of the event associated with that specific variable. The key proportional hazards assumption will be assessed by examining plots of the scaled Schoenfeld residuals against time for the covariates. Any non-random pattern indicates a violation of the proportional hazards assumptions in which case transformation of covariates may be considered. For example, all continuous variables were naturally logarithmically transformed to minimize the influence of extreme values and to

improve discrimination and calibration of the models. A parametric approach such as exponential or Weibull distribution for the hazard function can also be carried out. A total of 6 risk prediction models will be established for total CVD, all-cause mortality and each of 4 major DM complications. The log of the hazard ratio of each selected risk factor in the final model will be used as coefficient weights in the prediction model of each relevant outcome. The risk equations for 10 year's follow-up will be established by combining these weights with the survivor function(9). A receiver operating characteristic (ROC) curve of predicted risk against observed events will be used to determine the risk threshold for the predicted outcomes as the risk threshold with the highest sum of sensitivity and specificity of the actual observed events.

Validation of risk prediction models

To validate the risk prediction models for total CVD, all-cause mortality and each of 4 major DM complications, they will be applied to the data of the one third validation sample to estimate the risk level of the subjects. A receiver operating characteristic (ROC) curve of predicted risk against observed events will be used to calculate the area under the curve (AUC) for assessing overall prediction accuracy. The corresponding 95% confidence interval will be obtained by bootstrapping of size 2000. An AUC of less than 0.7 indicates limited discriminating power, 0.7 to 0.8 is acceptable, and higher than 0.8 suggests strong discrimination of the predictive models. Using the optimal prediction risk threshold identified by ROC curve in training dataset, and the corresponding sensitivity and specificity of the models against observed events will be calculated to further evaluate the performance of the models.

Calibration will be used to measure how closely predicted outcomes agree with actual outcomes. Calibration of the model's ability to correctly estimate the absolute risks will be examined by modified Hosmer-Lemeshow test and calibration plots. The modified Hosmer-Lemeshow test for time to event data measures how well the predicted probability of the expected event rate agrees with the observed event rate, where a *p*-value higher than 0.05 indicates good model calibration. In a calibration plot of the observed incidence of events against the predicted risk shows the scatter along the 45° line of perfect fit between predicted risk and observed incidence of event throughout the entire risk spectrum.

The D statistic, R^2 statistic and Brier score will be calculated for assessing the predictive power of the model. The D statistic is a measure of discrimination where higher value indicates better discrimination. The R^2 statistic is a measure of explained variation with a higher value indicating better performance. The Brier score is a measure of goodness of fit in which a lower value mean higher accuracy.

Development of a risk prediction nomogram and chart

In order to enable the 10-year risk prediction models for total CVD and all-cause mortality to be applied in busy clinical setting, risk prediction nomograms and charts will be developed for men and women. For the nomogram, the patient's score for each predictor is plotted on the appropriate scale and vertical lines are drawn to the line of points to obtain the corresponding scores. The score of each predictor will be transformed based on the estimated standardized beta coefficient of each predictor from the risk prediction model. For the continuous predictors (e.g. age), the line with interval depends on it units from minimum to maximum values among studies subjects (e.g. 20, 40, 60, 80 years old) will be displayed on the nomogram plot and the corresponding scores will be obtained based on the estimated standardized beta coefficient of the predictor (e.g. assign age of 20 to 0 point, age of 40 to 2 points, age of 60 to 4 points, age of 80 to 6 points). For categorical predictor (e.g. gender), each level of the predictor will be ranked a corresponding score based on the estimated standardized beta coefficient of the predictor (e.g. assign female to 0 point, male to 3 points). We have developed a similar nomogram on the risk of DM in a previous study as shown in Appendix C (24). All scores are summed to obtain a total score. The total score is plotted on the total line with corresponding predicted risk of CVD. Moreover, we will develop risk prediction charts similar to those developed by the Joint British Society as shown in Appendix D. The most significant predictors, up to a maximum of five, found in the full Cox regression models will be selected to classify subjects into 10-year CVD risk groups of <10% (low risk), 10%-20% (medium risk) and >20% (high risk). The Kaplan-Meier survival curves of each risk group will be developed and compared by log-rank tests to confirm the hazard ratios are significantly different among all risk groups.

STATA software version 13 (STATA Corp, College Station, Texas) will be used for data analyses. 5% is used as the level of significance in all statistical tests.

Strategies against anticipated problems

1. Missing data of risk factors

   Multiple imputation will be used to handle missing data. Multiple imputation aims at increasing the power of the analysis and producing more reliable and applicable models within clinical practice. It also takes subjects with incomplete data into account to avoid unnecessary biases. Each missing value will be imputed five times by the chained equation method, which was equivalent to attain a relative efficiency of 95%. For each of the five imputed datasets, the same analysis will be performed with the five sets of results combined based on Rubin's rules.

2. Misclassification bias from the use of administrative database

   This study relies on doctor entries of clinical diagnosis on DM complications and co-morbidity indicated by pre-defined by ICPC-2 and ICD-9-CM codes, which may be subject to misclassification bias. We will cross-check the diagnosis and prescription relation, and compare diagnosis from hospital and primary care records for the same patient in order to assess the data quality.

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e) Timetable of Work

June – August, 2017:
i. Recruitment, training of RA
ii. Meeting and discussion with HA co-investigators and Statistics team to confirm the data extraction schema and operation definitions

September – December, 2017
i. Extraction of data from HA CMS
ii. Update literature review

January – March, 2018:
i. Data cleaning
ii. Data analysis on the incidence & risk factors of DM complications and mortality

April – December, 2018:
i. Data analysis to develop 6 prediction models
ii. Validation of the prediction models

January -May 2019:
i. Development of 10-year CVD risk prediction nomograms
ii. Development of 10-year CVD risk prediction charts
iii. Preparation of manuscripts for publications
iv. Preparation of final report.

f) Existing Facilities:

The Department of Family Medicine and Primary Care (FMPC) has more than 20 years of experience in health services research. We have a dedicated team led by clinical academic staff and supported by postdoctoral fellows, statisticians and research assistants. Our research team has been commissioned, in collaboration with the HA, to carry out an extended evaluation of quality of care and effectiveness of five new chronic disease management programmes of the HA from 2012 to 2016. We have completed three evaluation and quality improvement cycles and built the preliminary CEA models for the two programmes as scheduled, and published 27 referenced journal papers. Our team has the expertise and computer facilities to handle a very large data base of over 200,000 patient records.

In our evaluation of QOC and effectiveness studies of the RAMP-DM and Patient Empowerment Programme (PEP) we have identified a cohort of 90,000 primary care DM patients and extracted their anonymized 5-year longitudinal data from 2008 to 2013, and showed the effectiveness of both RAMP-DM and PEP in improving clinical outcomes and reducing the incidence of 1-year and 3-year CVD complications in DM patients (7). We are confident that we can identify the required number of subjects from our existing cohort and extract the 10-year longitudinal data. (Dr Daniel Fong and Mr Eric Wan) are bio-statisticians who will lead the statistical analysis of the project, and we have previously managed and analyzed large datasets that include over 2 million records from over a hundred thousand individuals (7, 8, 22), and conducted risk prediction models leading to international journal publications (24, 25).

g) Justification of Requirements:

Proposed Budget (All costs are in HKD)

Item	**Description/Justification**	**Sub-total Cost**
1.Staff related costs		
one Full time Senior Research	Senior Research Assistant with expertise in medical statistics is needed to carry out the	$994,029

Assistant 0.5 Full time Research Assistant for one and half years	large amount of complex data analysis of longitudinal data, co-ordinate the whole project and liaise with the HA Statistics Department. HKD $32,950 (includes MPF) x 24 months = $790,800 Research Assistant is required to assist data cleaning, analysis, literature review and preparation of manuscripts and reports. HKD $22,581 (includes MPF) x 0.5 x 18 months = $203,229	
2.General Expenditure		
Service charge by the HA	For CMS data extraction by the Statistics Department of the HA	$150,000
Computers	One high speed & memory computer for handling a large database	$7,000
Statistical software	One license of STATA software (STATA Corp, College Station, Texas) are needed for the analysis of a large data set.	$7,000
Overseas conference	Conference attendance to disseminate results	$10,000
Publication fee		$20,000
Audit fee		$10,000
Printing and consumables		$1,971
Total:		$1,200,000

h) Purpose and Potential:

This study is strongly relevant to the thematic priority of “Enhancing multi-disciplinary health service models and effectiveness for primary care programmes in chronic disease management” of the Health & Health Services Research. There is a need for the development of 10-year risk prediction models based on the up-to-date population-based cohort for diabetic complications, particularly first total CVD. Chinese patients in primary care will enable accurate risk stratification, better prioritization of resources and more cost-effective interventions for diabetic patients in primary care. They can also better inform and empower patients to prevent potential DM complications. At the health policy level, the results can inform decisions on service provision in the care of diabetes mellitus in primary care to achieve maximum population health benefit. The prediction models can also be used as an outcome measure on the potential benefits of complication prevention in clinical trials on DM interventions in primary care.

i) Key References:

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