Protocol

China Diabetes Registry - a Prospective Cohort Study of Patients with Diabetes in National Metabolic Management Centers (MMC) in China

Study Protocol

(Version 2.1)

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1. Background

The prevalence of diabetes and its related disease burden was increased dramatically in the past decades. It showed that, according to the report from World Health Organization (WHO), the prevalence of diabetes was about 150 million around the world in 2000. With 6% increase every year, it is estimated to reach 300 million by the year 2025. This situation is worse in Asia, especially in China [1-3]. A general population-based survey, involving data from 98,658 adult individuals in China, using 2010 criteria of the American Diabetes Association (ADA), indicated that the prevalence of diabetes and prediabetes in Chinese adults was 11.6% and 50.1%, respectively [1]. These findings indicated that China has the largest absolute diabetes disease burden worldwide. This is followed by an increase in the country's economic burden and health care expenses for diabetes and its related complications. And this cost reached 30 billion and more every year, accounting for 8 percent of the health care cost in total. What is more frightening is that the economic expenditure on diabetes care is expected to increase in the future [4, 5].

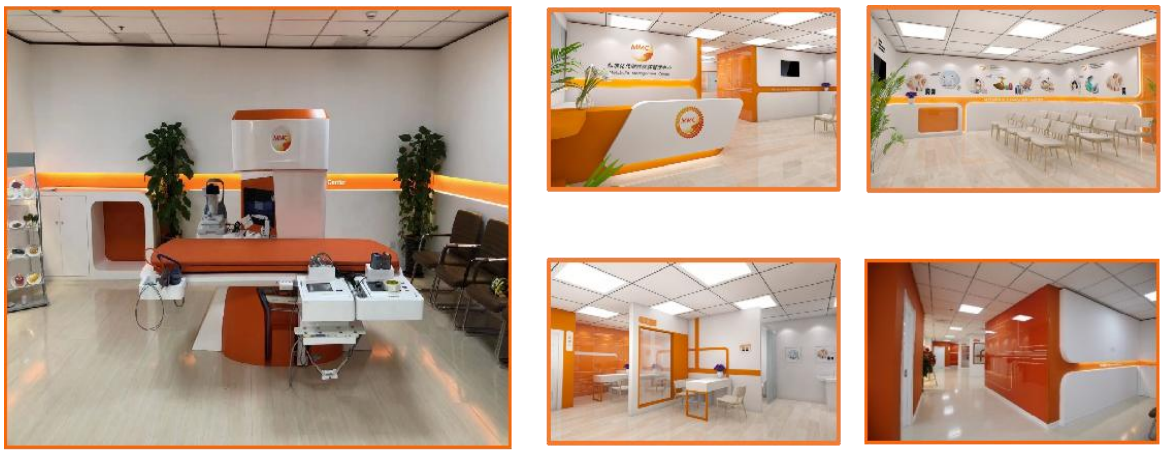
The reasons behind were complicated. However, rapid changes of lifestyle, social aging, and accelerated obesity might be the potential reasons for the increase in the incidence of diabetes [1, 6]. Moreover, China now faces several challenges when dealing with the problems in diabetes prevention and management. First, contrary to the high prevalence of diabetes, the rate of awareness and control of diabetes were relatively low and unsatisfactory. Extensive and efficient health education in the whole population is insufficient. Moreover, with the serious imbalance in the

physician to patient ratio, it is difficult to achieve early diagnosis and adequate care of diabetes and its complication. Second, the existing hospital facilities and management system can hardly meet the requirement of the quick increase in diabetes population. Inconvenient and time-consuming tests procedure make it difficult to diagnosis for diabetes and its complications. Moreover, according to the Healthy China 2030 strategy, the management of chronic diseases like diabetes should be handled at different levels, which was called a tiered medical services policy. However, there are difficulties in the implementation of this policy which might be caused by the wide variations in the economy, cultural, and medical service standards in different regions all around the country. Therefore, it is necessary to form a pilot and standard system, integrating with advanced technologies, which can be followed and copied in different regions nationwide, so as to deal with the challenges in management of diabetes and its related complications. Therefore, in 2016, the National Metabolic Management Center (MMC) was firstly established and promoted nationwide.

2. ONE CENTER, ONE STOP, AND ONE STANDARD MODEL IN THE MMC

All MMCs in China have the same structure in terms of facilities, layout, and databases, as well as the same routine daily operations, aiming to establish a platform with standardized diagnosis and treatment of metabolic diseases and their long-term follow-up. This platform of treatment is called the ‘One Center, One Stop, and One Standard Model’ (Figure 1). In the MMCs, patients can enjoy one-stop care to receive

a comprehensive series of services from registration, tests, evaluation, prescriptions, appointment follow-up, to health education. Under the guidance of the MMC Experts Committee, 492 stringent standard operational procedures (SOPs) are set up for quality control of the MMC operation (Figure 2). And we have also published MMC Guideline, Metbolic Disease Management Guideline for National Metbolic management Center which includes guidelines for diabetes diagnosis and treatment as well as the the process of management in MMC [7]. Furthermore, with technological innovations, for example, the “all-in-one machine” (Figure 1), by the ingenious integration of the examination equipments, greatly shortens the process for the screening of complications. In addition, the MMC has established an independent digital medical record system integrating real-time information of patients in and outside the hospital into a centralized medical data center that can be exported through various Internet of Things (IoT) instruments, including apps, Wechat, and a teleconsultation system, to enable patient care to be extended from the MMC to anytime, anywhere outside the center (Figure 3).

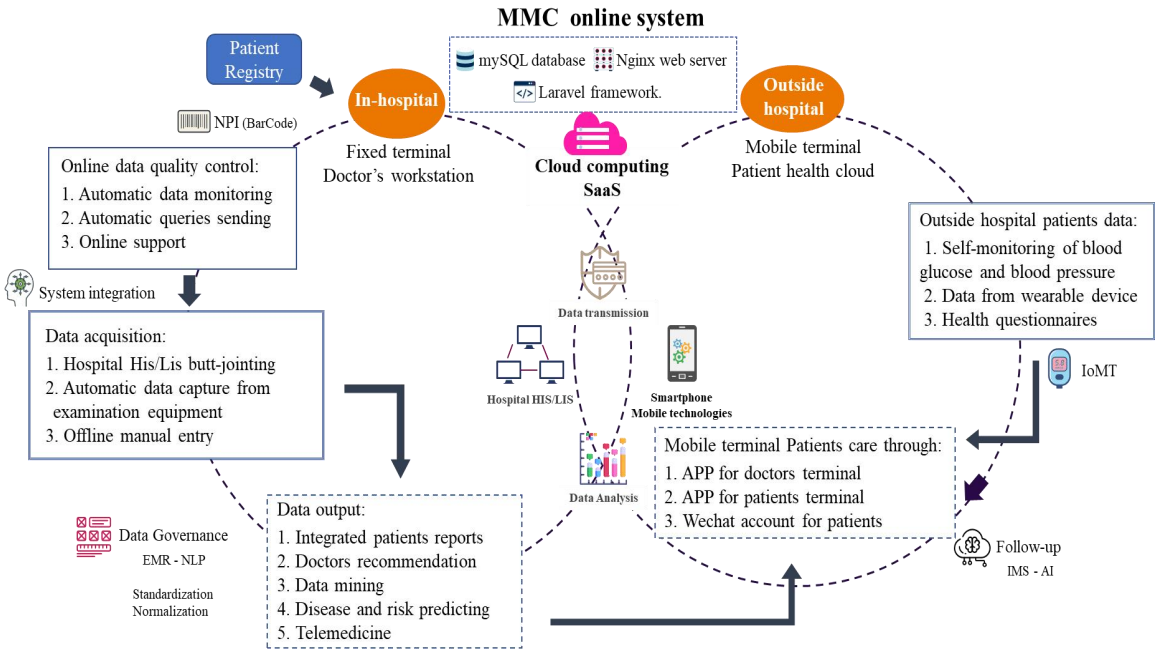


MMC "All-in-One" Machine

MMC "one-center, one-stop , one-standard" layout, unified nationwide

Figure 1. MMC's typical equipment and layout

Figure 2. Displays of MMC's SOP



NPI : National Patient Identifier; EMR, Electronic Medical Record; NLP, Natural Language Processing; SaaS, Software-as-a-Service; IoMT, Internet of Medical Thing; IMS, Intelligent management system; AI, Artificial Intelligence.

Figure 3. Internet-based electronic database management and patient care system for MMC program

3. Data collection

We encoded four metadata categories and devised numerous of data cleaning/conversion rules to create a proprietary electronic medical record system covering thousands of metabolic disease indicators. Leveraging HBee's intelligent HIS data acquisition, we gathered data on more than 1,000 examination/test indicators. Natural Language Processing (NLP) & Optical Character Recognition (OCR) in our MDoc engine analyze imaging reports, enhancing data quality. For unequipped MMCs, manual data entry and registration ensure complete data collection. During our data analysis, we ensure the desensitization of sensitive information related to patients' personal privacy.

4. OBJECTIVE AND LONG-TERM VISION OF THE MMC

The objective of the MMC is to launch a new metabolic disease management model based on the Internet health information platform. Moreover, the MMC helps improve adherence to and the effectiveness of treatment for patients, thus benefitting both patients and doctors. The proprietary electronic medical database in the MMC will make dynamic big-data analysis in diabetes epidemiology, prevention, diagnosis, and treatment very efficient and effective. Furthermore, this nationwide standardized care system also forms a collaborative research network for prospective interventional studies on treatment and prevention. Therefore, in the long run, the MMC will offer large amounts of data and evidence from hospital-based care to achieve long-term optimal health outcomes, enabling a replicable standard care model across the entire country that can form the base for future healthcare policy improvement.

Objective

1. To establish a multi-center nationwide prospective database of diabetes patients in MMCs, including clinical data, biological samples library so as to explore the epidemiology, genetics, new biomarkers, risk factors, and prognostic methods related to diabetes and its complications, as well as other metabolic diseases.

2. To collect cross-sectional data from patients seen and treated at each MMC centers so as to evaluate: the current status of care of patients with diabetes and its related complications, as well as other risk factors treatment strategies at these centers. Patients' costs and quality of life (QoL) will also be evaluated.

3. To collect the prospective data of patients treated at each MMC centers in order to evaluate the strategies for the achievement of treatment goals, changes in management, control of risk factors, incidence and progression of all-diabetes related clinical endpoints (including mortality), behavioral changes, psychological well-being as well as costs and QoL.

5. Study Population:

All the patients who are seen and treated at each MMC centers, and meet the Inclusion/Exclusion Criteria will be included in this study.

Main Inclusion Criteria:

- Age ≥ 18 years old
- Diagnosis of diabetes according to the diagnostic criteria for diabetes at the time of enrollment.
- Gender: males and females
- Fully understand the study and provide written informed consent

- With satisfactory compliance

Main Exclusion Criteria:

- Patients with significantly reduced life expectancy (less than 5 years)
- With Drug abuse
- With Acquired Immune Deficiency Syndrome (AIDS) or syphilis or infectious diseases such as viral hepatitis or tuberculosis in active phase at enrollment

6. Questionnaires

6.1 Questionnaire Overview

Both baseline and follow-up questionnaires were designed to comprehensively collect metabolic diseases-related information. The questionnaires integrated the basic history collection requirements with the routine items of cohort studies in the area of diabetes [8, 9] and enabled us to examine modifiable and unmodifiable factors. All these data were collected through a proprietary electronic medical record system in MMC [10].

6.2 Questionnaire Implementation

All the questionnaire information can be collected by trained staff after informed consent. Furthermore, part of the questionnaire can be filled in by the patients themselves (patient-side) through downloading the MMC APP under guidance. The completed patient-side questionnaire (e.g., general information, symptoms, part of the medical history) needs to be checked and confirmed by the staff to guarantee the accuracy and authenticity.

6.3 the Baseline Questionnaire

The required baseline questionnaire can be subdivided into the following sections: general information, medical history, family history (cancer, diabetes, cardiovascular diseases, obesity and hyperlipidemia), symptoms, medication use, menstrual and reproductive history (e.g., for females, the menopausal history), birth and feeding history, lifestyle exposures and pregnancy (for women of childbearing age). The questions assessed in each required section are listed in Table 1. The other optional chapters for the baseline questionnaire such as basic knowledge structure of diabetes, diabetic psychology, diabetes skills and abilities (e.g., EuroQol Five Dimensions Questionnaire [EQ-5D]) will also be obtained.

Table 1. Required questionnaire data collected in each MMC (according to follow-up visits arranged within each year)

	Arranged follow-up visits				
Variables	Baseline	Month 3	Month 6	Month 9	Year 1
General information					
Unique identifier	√				
Birthdate	√				
Sex	√				
Ethnicity	√				
Origin and birthplace	√				
Blood type	√				
Education level	√				
Retirement status	√				
Occupation	√				
Economic level	√				
Marital status	√				
Whether the spouse has joined MMC	√				
Medical history					
Diabetes mellitus	√				

Hypertension	√				
Hyperlipidemia	√				
Coronary artery disease	√				
Stroke	√				
Heart failure	√				
Tumor	√				
Peripheral artery disease	√				
History of trauma and surgery	√				
Other diseases	√				
Symptoms	√				√
Family history	√				
Medication use	√	√	√	√	√
Menstrual and reproductive history (for females)	√				
Birth and feeding history	√				
Lifestyle exposures					
Smoking	√				√
Alcohol consumption	√				√
Dietary habit	√				√
Physical activity	√				√
Sleep	√				√
Pregnancy (for females)	If applicable	If applicable	If applicable	If applicable	If applicable
Adverse events		√	√	√	√

6.3.1 General Information

Multiple demographic and socioeconomic questions have been included (Table 1). Education level is defined as below high school, or high school and above. The unique identifier can be used not only to identify different patients, but also to capture data. In addition, the telephone number is required for registration, which is essential for telephone follow-up and access to the text message of appointment.

6.3.2 Medical History

The information collected in the section of medical history is shown in Table 1. The diagnosis of diabetes is confirmed if the participant has a self-reported history of diagnosed diabetes by professionals, and/or fasting blood glucose (FBG) ≥ 7.0 mmol/L, and/or 2h postprandial blood glucose (PBG) ≥ 11.1 mmol/L according to the 1999 World Health Organization (WHO) diagnostic criteria [11]. Since 2021, glycated hemoglobin (HbA1c) ≥ 6.5% was added into the diagnostic criteria for diabetes in accordance with 2020 guidelines for the prevention and treatment of type 2 diabetes in China. The duration of diabetes is determined by the following criterion: 1) the accurate time diagnosed with diabetes patients provided; 2) Newly diagnosed with diabetes (patients reported never diagnosed with diabetes before), the duration of diabetes is "0"; 3) if the information of whether diagnosed with diabetes before is not available and the laboratory examination meets the criterion of diabetes, the information of diabetic duration is missing.

1) Types of diabetes

At each MMC, a qualified medical practitioner was responsible for determining the specific type of diabetes. Participants with type 1 diabetes (T1DM), gestational diabetes mellitus (GDM), and other specific forms of diabetes were excluded from the study. In cases where the type of diabetes was unclear, T1DM was diagnosed based on the presence of glutamic acid decarboxylase antibodies (GADA) and low C-peptide concentrations (<0.8 ng/mL). A comprehensive review of medical records and laboratory tests, including thyroid and adrenal hormone profiles, and other

relevant parameters, was conducted to exclude rare or unusual cases of diabetes. For a more detailed account of these diagnostic procedures, please refer to our previously published article [12].

2) Other metabolic related disease

(1) Hypertension: Ever diagnosed by physicians; or when measuring the clinic blood pressure on three different days without the use of antihypertensive medications, systolic blood pressure (SBP) is ⩾140mmHg and/or diastolic blood pressure (DBP) is ⩾90mmHg. If a patient has a history of hypertension and is currently taking antihypertensive medications, even if their blood pressure is lower than 140/90mmHg, they should still be diagnosed with hypertension.

(2) Hyperlipidemia: Ever diagnosed by physicians; or when enrolled in MMC, laboratory tests showed LDL-C ⩾ 3.4 mmol/L (130 mg/dl) and / or TG⩾1.7 mmol/L (150 mg/dl).

(3) The prevalent cardiovascular diseases are defined as meeting any of these conditions: (a) stroke or (b) myocardial infarction or other coronary heart disease or (c) heart failure. Please refer to the “9. Clinical Outcome Measures” for details.

6.3.3 Medication Use

All medications which have been used regularly in the recent 3 months before enrollment are required to be registered, which include glucose-lowering, antihypertensive, and lipid -lowering drugs and other drugs. The staff record usage, dosage, start date, end date, adjustment date of each agent in detail, which can meet

the wide range of needs for scientific research.

6.3.4 Lifestyle Exposures

The lifestyle information encompasses smoking, alcohol, dietary habits, physical activities as well as sleep. The smoking and drinking sections contain questions relating to smoking/drinking habits (at present and in the past), amount, type, as well as duration. The current smoking and drinking status are defined as "yes" if the frequency is daily (or almost daily) and weekly (or almost weekly), respectively. We also define ideal smoking if the participant has never smoked or stopped smoking for more than 12 months.[13] Definition about smoking and drinking habits may be changed in certain analysis.

In the dietary part, we collect the usual dietary intake during the past 12 months. The dietary questionnaire evaluated in China Noncommunicable Disease and Risk Factor Surveillance and the Risk Evaluation of Cancers in Chinese Diabetic Individuals (REACTION) study [8, 9] was simplified and adapted to be suitable for real-world clinical settings. The diet components that have greater evidence regarding their close association with metabolic diseases were retained, and a semi-quantitative design was adopted. The questionnaire involves the following food items: fresh fruits, fresh vegetables, fish, soy products, salt and sweets/sugar-sweetened beverages. Adapted from the American Heart Association (AHA) 2020 Impact goals [13], a diet score can be calculated based on the following five healthy diet components: more intake for fruits and vegetables (≥4.5 cups/d), fish (≥two 3.5-oz servings/week), and soy protein (≥25 g/d), less intake for salt (< 4g/d salt) and sweets/sugar-sweetened

beverages [14]. Other definitions for low salt intake (≤6g/d or ≤8g/d salt) are also explored for their relation to clinical outcome measures. The U.S. Department of Agriculture (USDA) nutrition plate is referred for details.

The level of physical activities at work and leisure time is obtained. With respect to physical activity at leisure time, the International Physical Activity Questionnaire (IPAQ) is adopted [15], which records physical activity in terms of intensity, frequency and duration. It is a healthy lifestyle behavior if the participant performs ≥150 min/week of moderate-intensity physical activity, ≥75 min/week of vigorous-intensity physical activity, or ≥150 min/week of moderate-intensity and vigorous-intensity physical activity. In addition, the quality and duration of sleep are also surveyed.

6.4 Follow-up Questionnaires

Planned follow-up surveys will be conducted every 3 months from baseline. The follow-up questionnaires are specified in standard operating procedures (SOPs) and presented in Table 1 (taking one year as an example). Symptoms and lifestyle factors will be collected at one-year interval. For each follow-up visit, patients' actual medication use and adverse events (with pre-defined categories of diseases) needs to be recorded repeatedly and registered in the electronic medical record system. Adverse events refer to any adverse medical events that occur during the patient's visit, which could be any unwell sign, symptom, disease, or laboratory abnormality. The registered adverse events mainly include cardio-cerebrovascular events, severe hypoglycemia, cancer, hospitalization, laser coagulation treatment for diabetic

retinopathy (DR), and other adverse events that local doctors judge necessary to record. Details are formulated in the corresponding chapter ('Assessing and Recording of Adverse Events').

For patients who have been lost to facility-based follow-up, the staff will be proposed to make a telephone follow-up. If the call gets through and death is learned, death registration (e.g., date, causes of death) will be completed by the staff. Hospital records and death certificates will be supplemented if available.

7. Physical Measurements

Height, weight and blood pressure are recorded at each visit. Head circumference is obtained at the baseline visit without repeated measurements later. Circumferences of neck, waist and hip, visceral fat area (VFA) and subcutaneous fat area (SFA) are recorded once a year. VFA and SFA measurements is required for regional MMC, and optional for county and community MMC (Table 2).

Table 2. The required items for physical measurements and clinical examination in different levels of MMC (according to follow-up visits arranged within each year)

Variables	Arranged follow-up visits				
	Baseline	Month 3*	Month 6	Month 9*	Year 1
Physical measurements					
Height and weight	□○△	□○△	□○△	□○△	□○△
Blood pressure and heart rate	□○△	□○△	□○△	□○△	□○△
Head circumference	□○△				
Neck, waist and hip circumference	□○△				□○△
VFA and SFA	□				□
Laboratory tests					
Blood and urine routine	□○△				□○△
Biochemical tests	□○△	□○△	□○△	□○△	□○△
HbA1c	□○△	□○△	□○△	□○△	□○△

FBG	□○△	□○△	□○△	□○△	□○△
PBG	□○△				□○△
Fasting serum insulin/C-peptide	□○				□○
Postprandial insulin/C-peptide	□○				□○
UACR	□○△		□○△		□○△
Islet autoantibodies	□				
Thyroid hormone	□				
Examination of diabetes-related complications					
Fundus examination	□○△				□○△
Screening for diabetic neuropathy	□○				□○
Measurements of baPWV and ABI	□○				
ECG	□○				
Echocardiogram	□○				
Carotid Ultrasonography	□○				

□,○,△: representing the requirements for regional, county, and community MMC, respectively; * denotes the visits not required by quality control; VFA: visceral fat area; SFA: subcutaneous fat area; HbA1c, glycated hemoglobin; FBG, fasting blood glucose; PBG, postprandial blood glucose; UACR, urinary albumin-to-creatinine ratio; baPWV, brachial-ankle pulse wave velocity; ABI, ankle-brachial index.

7.1 Height and Weight

Height and body weight will be measured by a height-weight scale with participants removing shoes and heavy outer clothing. Several parameters which are accurate to one decimal place including height in centimetres, weight in kilograms and BMI calculated as the weight in kilograms divided by height in meters squared will be displayed on the screen.

7.2 Head, Neck, Waist and Hip Circumference

In addition to height and weight, the patient's head, neck, waist, and hip

circumference should also be measured. Head circumference will be measured by a measuring tape through superciliary arch (just above the eyebrows) and occipital protuberance. Neck circumference will be recorded below the laryngeal prominence. Waist circumference will be measured midway between lateral lower ribs and the upper margin of the iliac crest for standing participants. Hip circumference is the maximal width of the buttocks. The staff have been trained to ensure that the measurements can be performed correctly. All measurements will be accurate to one decimal place.

7.3 Blood Pressure

After at least a 5-minute rest, blood pressure and heart rate will be measured using an automated electronic device in the seated position. The elbow of the arm used for measurement need to be supported at heart level. The monitor will automatically upload the systolic and diastolic blood pressure and heart rate readings to the MMC electronic database system.

7.4 Visceral and Subcutaneous Fat

VFA and SFA will be measured by a dual bioelectrical impedance analyzer (DUALSCAN, HDS2000, Omron Healthcare Co.). An abdominal measuring device will be attached around the abdomen at the umbilical level to measure abdominal shape, so as to calculate the total abdominal cross-sectional area. The fat-free area is calculated by the axial abdominal impedance generated when the current flows through the four limbs by four electrodes on hands and feet. When a current is applied to eight electrodes placed at the level of umbilicus, the measured abdominal surface

impedance is used to calculate SFA. SFA and fat-free area is finally subtracted from the total abdominal cross-sectional area to calculate VFA. The visceral fat increase is defined as VFA ≥100 cm^2 or otherwise specified.

8. Clinical Examination

The organizational structure of MMC consists of the MMC leading center, regional centers, county centers, and community centers. Different setting standards for MMCs at each level have been described in detail in the guide[16]. Overall, comprehensive laboratory tests and examination of complications related to diabetes are carried out at baseline and annual visits in regional or county MMC. It is proposed to refer the patients at community MMCs to regional or county MMCs nearby at initial and subsequent annual visits for comprehensive examination. Follow-up visits are implemented to record patients' clinical progress, thereby providing important information for establishing and modulating treatment strategies. Schedules for clinical examinations at each visit during one year can be found in Table 2.

8.1 Baseline Laboratory Tests

The required baseline laboratory tests at different levels of MMC are shown in Table 2. Islet autoantibodies mainly involve insulin cell antibody (ICA), insulin autoantibody (IAA) and glutamic acid decarboxylase antibody (GAD-Ab), and it is proposed to detect GAD-Ab at least to help classify the type of diabetes. All laboratory tests will be performed in local sites.

8.1.1 HbA1c Measurements

Local HbA1c for regional and county MMCs should be measured by

high-performance liquid chromatography (HPLC).

8.1.2 Glucose Tolerance Test

For the glucose tolerance test, participants will be required to fast overnight to undergo a standard steamed bread meal test. First, at fasting, blood is drawn for measuring fasting blood glucose (FBG), fasting serum C peptide and/or insulin, liver and kidney function, blood lipid profiles and other laboratory tests. For postprandial measurements, 100 g steamed bun will be given. After the first bite, the patients will have blood drawn 2 hours later in order to measure postprandial blood glucose (PBG), postprandial serum C peptide and insulin. Under certain circumstances, 3h oral glucose tolerance test (OGTT) in five time points will be undertaken. Participants are forbidden to smoke, drink or eat anything throughout the glucose tolerance test. Patients who have been diagnosed with diabetes take their hypoglycemic and other agents normally during the test.

8.2 Baseline Examination of Diabetes-related Complications

8.2.1 Fundus Photography

Fundus examination is performed for all diabetic patients by an experienced and trained technician. One color macula-centered fundus image will be acquired from each eye. Fundus images are taken without pupil dilation and with a 45-degree field of view. The worse diabetic retinopathy (DR) classification of the two eyes will be chosen as the final patient-level DR grade. The status of DR is defined as “yes” if mild non-proliferative DR (NPDR) or above is present. We describe DR grade by

following definitions: referable DR (moderate NPDR or above); vision-threatening DR (VTDR, severe NPDR or above and/or clinically significant macular edema [CSME])[12]. The definition for VTDR may be modulated and specified in certain studies.

8.2.2 Screening for Diabetic Neuropathy

To assess diabetic peripheral neuropathy (DPN), electromyography is prioritized in hospitals where conditions are available. The instrument (NC-stat® DPN Check™) can also be used to measure the amplitude and conduction velocity (CV) of the sural nerve in legs of the patient. The amplitude has been found to decrease by about 1 μV per decade with age. Sural nerve conduction velocity is correlated with age and height, decreasing by 1.3 m/s per 10 years and 2.0 m/s per 10 cm height. After entering age and height, the device will automatically determine the status of DPN (normal, mild, moderate or severe) according to the levels of amplitude and CV with reference to the calculated normal limit.

8.2.3 Measurements of brachial-ankle pulse wave velocity (baPWV) and ankle-brachial index (ABI)

The noninvasive measurements of baPWV and ABI will be performed using an automated recording apparatus (BP-203RPE III, form PWV/ABI or HBP-8000, Omron Healthcare Co.) in the supine position after resting for at least 5 minutes[17]. Suitable cuffs will be attached to participants around both arms and ankles to take measurements of both the brachial and tibial arteries by a trained operator. BaPWV values will be calculated as dividing the transit distance (the distance from the heart to

the ankle minus the distance from the heart to the arm) by the transmission time, which equals to the time interval from the initial increase in the brachial to that of tibial artery waveforms[18]. The mean or greater value of the right and left baPWV will be analyzed. Generally, the upper quartile of baPWV is defined as arterial stiffness. The systolic blood pressure (SBP) at the ankle is divided by the SBP at the upper arm to calculate the indicator ABI, which is used to screen peripheral arterial disease.

8.2.4 Carotid Ultrasonography

Carotid intima-media thickness (IMT) as well as plaques is examined using a Doppler apparatus. The location to measure IMT of the common carotid artery (C-IMT) is the distal wall of the common carotid artery, 10 mm proximal to the bifurcation[19]. An average or larger value of C-IMT on the left and right sides will be recorded for analysis. Carotid plaque will be determined as “yes” if the plaque is present in either side of the carotid and its branches.

8.2.5 Electrocardiogram (ECG) and Echocardiogram

The patients will undergo ECG and echocardiographic examinations to detect cardiac abnormalities. Structured report will be recorded for analysis. In the ECG report, the cardiac rhythm and diagnosis will be required to record. In the echocardiographic report, besides the final diagnosis information, the following parameters will also be obtained: left atrial diameter (LAD), interventricular septal thickness, left ventricular internal diameter in systole and diastole, posterior wall thickness of left ventricle, left ventricular ejection fraction (LVEF), and inner diameter of aortic root.

8.3 Clinical Examination at Follow-up Visits

According to the standard protocol, two to four follow-up visits every year are arranged for enrolled patients, with the same follow-up frequency formulated for regional, county, or community MMCs. The actual number of visits may be changed depending on patients' condition and compliance. The flow chart for clinical examination at each visit within one-year period are listed in Table 2. The clinical examination in the follow-up stage beyond one year are also performed with reference to Table 2.

Urinary albumin-to-creatinine ratio (UACR) will be collected every six months to define the status of proteinuria. Fundus photography and screening for diabetic neuropathy will be performed annually. The patients with moderate DR or worse will be referred to the ophthalmology department for further examination and treatment. Carotid ultrasonography, baPWV and ABI will be evaluated at least 3 times during the 5-year follow-up period (baseline, year 2 or year 3, and year 5). ECG and echocardiogram will be arranged at least twice within 5 years (baseline and year 5). The screening frequency of diabetes related complications may be adjusted if necessary.

9. Clinical Outcome Measures

9.1 Primary outcome measures: The primary outcomes include incidence of all diabetes-related clinical endpoints:

1) Mortality
   (1) Total mortality;
   (2) Cardiovascular mortality: includes fatal myocardial infarction (MI), death due

to stroke, fatal congestive heart failure, unexpected death presumed to be due to ischemic cardiovascular disease, death due to documented arrhythmia, and death due to other cardiovascular diseases;

(3) Fatal renal failure

2) The Macrovascular morbidity

(1) Coronary heart disease

a) non-fatal MI or ischaemic heart disease

b) Coronary revascularization or coronary artery bypass surgery

c) Percutaneous transluminal coronary angioplasty (PTCA)

(2) Carotid angioplasty with or without stent; Carotid endarterectomy

(3) Peripheral vascular disease

a) Peripheral angioplasty with or without stent;

b) Peripheral vascular surgery (including aortic aneurysm repair);

c) Peripheral circulatory disorders;

d) Peripheral vascular disease;

e) Limb amputation due to vascular disease;

f) Gangrene.

(4) Stroke

a) Ischaemic stroke (a nonvascular etiology must be absent);

b) Intracerebral haemorrhage;

c) Subarachnoid haemorrhage;

d) Other and unspecified intracranial haemorrhage;

e) Stroke of unknown type etiology.

3) Non-fatal congestive heart failure

4) The Microvascular morbidity

(1) Diabetic kidney disease (DKD):

a) Chronic kidney disease: Estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 (as estimated by the EPI equation, eGFR=141 × min(Scr/κ, 1)$^{\alpha}$ × max(Scr/κ, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 [if female] _ 1.159

[if black], where Scr is serum creatinine in mg/dl, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min represents the minimum of Scr/κ or 1, and max represents the maximum of Scr/κ or 1).

b) End-stage renal disease: Estimated glomerular filtration rate (eGFR) <15 ml/min/1.73m^2, or need dialysis, or need renal transplant

c) Development of microalbuminuria (urinary albumin/creatinine ratio [UACR] ⩾30 and < 300mg albumin per gram creatinine, or UACR ⩾ 3.39 and < 33.9 mg/mmol in a random sample)

d) Development of macroalbuminuria (urinary albumin/creatinine ratio [UACR] ⩾ 300mg albumin per gram creatinine, or UACR ⩾ 33.9 mg/mmol in a random sample)

(2) Diabetic retinopathy (DR):

a) If both eyes' images were evaluable, the more severe DR grade between the two was adopted.

b) If only one eye's image was gradable, the DR grading relied solely on that eye.

c) If no gradable image was available for either eye, the patient was classified as ungradable.

d) In cases of discrepancy between the on-site and qualified AI result, the more severe DR grade was selected.

e) Any occurrence of the following adverse events was classified as an incidence of DR: undergoing laser treatment or therapy with anti-vascular endothelial growth factor (VEGF) inhibitors, experiencing vitreous/preretinal hemorrhage, clinically significant macular edema (CSME), undergoing vitrectomy, or developing diabetes-related blindness.

5) Neuropathy

6) Cancer:

The occurrence of any of the cancers include prostate, breast, lung/bronchus, endometrial, colon, gastric, leukemia, lymphoma, pancreas, kidney/renal pelvis, rectal, and melanoma;

7) Major infections: include chronic and acute infections, pulmonary and non-pulmonary;
8) Hospitalization for any of the above reasons.

9.2 Secondary Outcome Measures:

1) Glycated haemoglobin (HbA1c, %)
2) Fasting and postprandial glucose concentrations (mmol/L)
3) fasting and 2-hour postprandialinsulin and C peptide levels, as well as the variables derived from these measurements (homeostasis model assessment index for assessing insulin resistance [HOMA-IR and HOMA2-IR]
4) Lipids levels include triglyceride, total cholesterol, high density lipoprotein-cholesterol (HDL-c) and low density lipoprotein-cholesterol (LDL-c)
5) Blood pressures (mmHg)
6) Body weight, and BMI: Body weight (kg) and height (m) will be combined to report BMI in kg/m^2
7) Visceral fat (cm^2) and subcutaneous fat (cm^2)
8) Health related quality of life
9) Cognitive function
10) Other anthropometric parameters, include head, neck, waist, and hip circumferences
11) Carotid plaque and carotid intima-media thickness;
12) Brachial-ankle pulse wave velocity (baPWV) and ankle-brachial pressure index (ABI)
13) Psychological well being, using physiological parameter, questionnaire
14) The incremental cost per quality adjusted life year (QALY) gained. QALYs will be measured by the EuroQol-5 Dimensions (EQ-5D) questionnaire.

9.3 Safety measures:

1) Hypoglycemia: any hypoglycemic episode (blood glucose concentration <70 mg/dl [3.9 mmol/l]), and severe hypoglycemic episodes requiring third party assistance;
2) The alterations of vital signs, 12-lead ECG,
3) Laboratory abnormalities, include blood biochemistry, blood and urine routine measures;
4) Adverse events (type, frequency, severity, relationship of adverse events to drug therapies).

9.4 Exploratory measures:

Explore the epidemiology, genetics, new biomarkers, risk factors, and prognostic methods related to diabetes and its related complications, as well as other metabolic diseases.

10. Quality assurance and quality control measures for clinical operation

The MMC's four-tiered prevention and control network infrastructure consists of the MMC leading center (MMC in Ruijin hospital, Shanghai Jiao Tong University School of Medicine, Shanghai), regional centers, county centers, and community centers (Figure 4). The MMC leading center establishes a comprehensive set of written standard operating procedures (SOPs), which are then provided to all MMCs to ensure quality assurance (QA) throughout every stage, from site construction to clinical operations. This ensures a uniform and high-quality approach to disease management across the entire network.

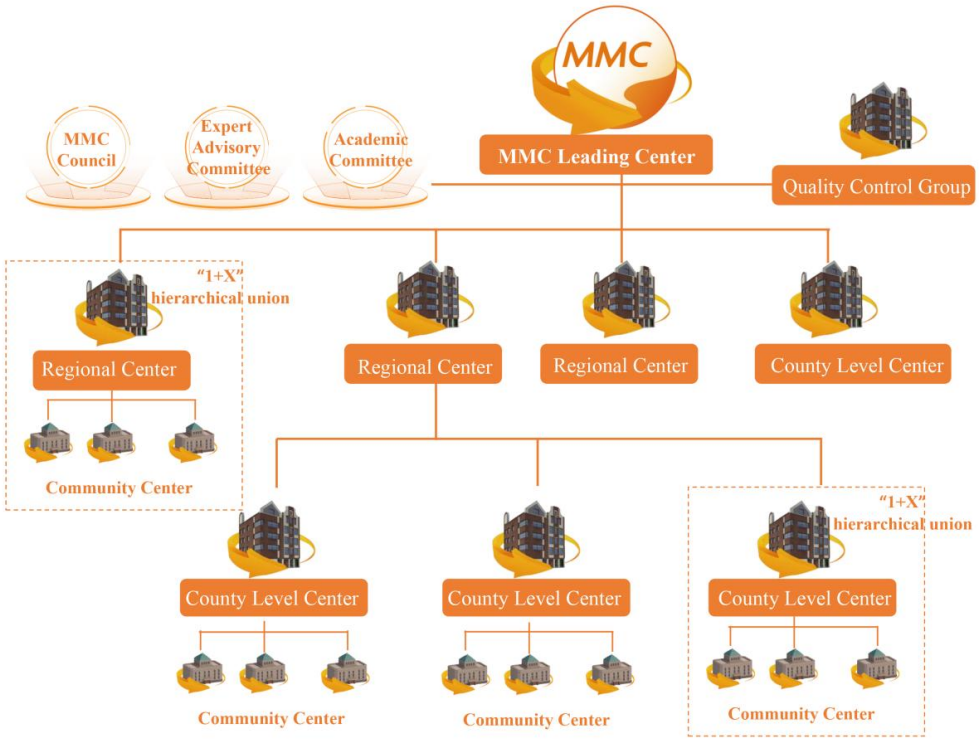


Figure 4. MMC four-level prevention and control network infrastructure

During the initial stage, all staff members in each center, encompassing doctors, nurses, and technicians, will undergo comprehensive training via the MMC's specialized internet-based SOPs training platform. Engineers will also be responsible for conducting on-site training sessions to ensure proficiency in equipment operation. It is mandatory for the center staff to complete all relevant online courses and pass the subsequent examination receiving certification of qualification before commencing patient enrollment (Figure 5).

Figure 5. Certificate of qualification awarded to MMC staff after training

An independent electronic system for data acquisition, tracking, and management has been developed. This system provides real-time and automatic monitoring of data, enabling the prompt detection of any abnormal or out-of-range values. In such cases, the platform automatically sends correction reminders or queries to alert center staff. This prompts them to review data entries and make timely corrections. Additionally, to facilitate constant quality improvement across all centers, a free online support service and a WeChat working group are available to provide prompt assistance and solutions to any arising issues.

Once the baseline data entries for the initial 20 consecutive patients in each center have been completed, the quality control (QC) team from the MMC leading center will promptly conduct a remote data quality evaluation. Feedback and any queries arising from this evaluation will be promptly communicated to the respective centers for correction. Following the completion of baseline data entry for 200 consecutive patients, a second remote manual QC will be carried out to assess the operational quality and facilitate center certification. Once these steps are completed, each center will be subject to regular and ongoing data monitoring. Additionally, an automated monthly online QC report will be generated and made available online to ensure consistent operational quality across all centers.

An offline QC process has been established to guarantee precise clinical operations. First, each center is required to have a dedicated local QC staff member who will conduct a self-assessment based on the established SOPs and monthly QC reports, making necessary corrections as identified. Second, a clinical research associate from a third-party organization will conduct regular on-site monitoring. This includes checking clinical procedures, sample collection methods, verifying the consistency of source data with original medical records and online entries, as well as monitoring the follow-up process. Third, well-performing MMCs regularly hold sharing sessions to disseminate their experiences to other MMCs (Figure 6).

Furthermore, audits conducted by specialists from the MMC Quality Control Group will be conducted regularly to oversee both the standardization of facilities and workflow, as well as the operational procedures of staff members in each center. These audits ensure the maintenance of high-quality standards across all centers.

Figure 6. MMC online and off-line training, experience sharing

To evaluate and enhance the overall quality of the centers, an annual quality ranking will be performed for all centers nationwide. This ranking will be based on various metrics, including the center's participant enrollment capacity, the quality of clinical data, the follow-up rate of participants, and their overall management abilities.

The superior centers will be awarded an honorary certificate (Figure 7). Centers that fail to pass the quality assessment for two consecutive years will be required to undergo rectification and improvement measures. Centers that fail to pass the re-assessment process after rectification will not be recertified, thus will be not allowed to be involved in subsequent scientific research analysis. This ensures that only centers meeting the highest standards of quality are certified and continue to participate in the program.

Figure 7. Certificate awarded to superior MMCs

11. Geographical disparity

All patients are respectively divided into seven regions according to the location of MMC they MMC they enrolled (Table 3).

Table 3. Provinces/autonomous region/municipality in 7 regions of China

Region	Provinces
East China	Shanghai, Jiangsu, Zhejiang, Anhui, Fujian, Jiangxi, Shangdong, Taiwan
South China	Guangdong, Guangxi, Hainan, Hong kong, Macao
North China	Beijing, Tianjin, Shanxi, Heibei, Inner Mongolia
Central China	Henan, Hubei, Hunan
Northeast	Heilongjiang, Jilin, Liaoning
Southwest	Sichuan, Guizhou, Yunnan, Chongqing, Tibet
Northwest	Shaanxi, Gansu, Qinghai, Ningxia, Xinjiang

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