AP1: RESEARCH PROTOCOL TEMPLATE

Purpose:

The purpose of the template is to assist investigators and study personnel to

- formulate a protocol for proposed research
- consider all required elements of a protocol in the design of the research
- ensure that all protocols are formatted in a consistent manner

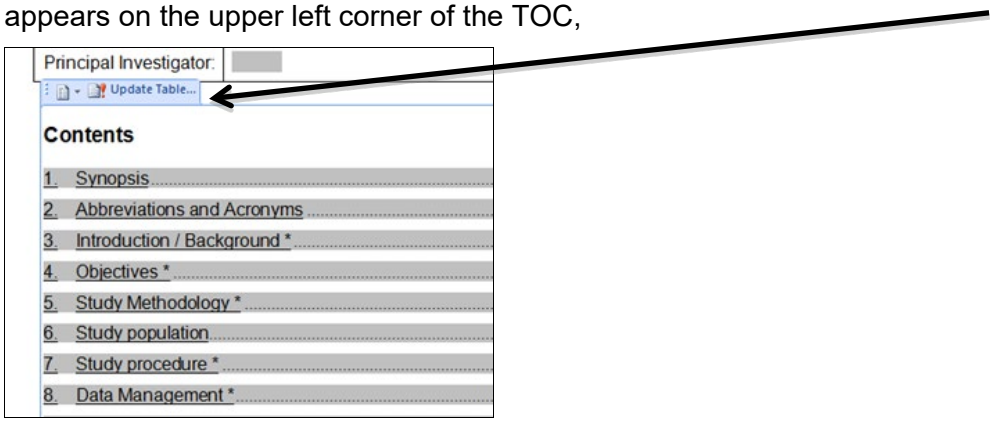
Directions for Completing the Protocol Template

1. Enter information in shaded areas
2. Enter MRC # for proposed research, if one has not been allocated, indicate that it is pending
3. Enter the name of the proposed research study.

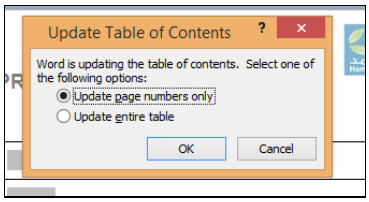
   Title should be very descriptive of the hypothesis of the proposed research. Always use the title designated in the protocol for all research applications, submissions and funding requests.
4. Enter the name of the Principal Investigator (PI), there is only **1** PI per research protocol (Application forms to the MRC, IRB and other departments will permit the listing of Co-PIs)
5. Refer to Protocol Guidance document for detailed information on each section of the protocol.

Directions for Updating the Protocol "Table of Contents" (TOC)

1. Once the Protocol is completed, the "Table of Contents" will need to be updated
2. Place cursor over the "Table of Contents", the area will highlight itself as a box (it should show up as light blue)
3. With the curser in this area, click a button on the mouse and an "Update Table" button appears on the upper left corner of the TOC,



4. With the cursor on "Update Table", click mouse, and a selection will appear that asks



5. Select "Update entire table" or "Update page numbers only" as appropriate
6. Select OK, Save and Rename document
7. The name of the document must be a name that identifies what the document is.

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RESEARCH PROTOCOL TEMPLATE

i.e. 12345_Protocol_v1

HMC RESEARCH PROTOCOL

MRC#:	17292
Study Title:	Qatar Diabetes Mobile Application Trial (QDMAT)
Principal Investigator:	Dr Noor Nabeel M. Suleiman

Contents

1. Synopsis*

In this section provide a brief summary of the research study (250-300 words).
The synopsis consists of 1-2 sentences of background, then a concise objective for the research followed by a brief description of research participants, interventions, methods, data collected and proposed analysis ending with the anticipated outcome(s).
Someone who knows nothing about the research should be able to get a clear snap shot of the proposed research and intend outcome.

Diabetes mobile technology is an emerging and rapidly expanding field that seeks to combine cutting-edge behavioral insights with best practice in diabetes self-management education to improve patient empowerment and deliver better patient outcomes. It is not yet clear if mobile applications are effective in improving glycemic control, clinical outcomes, quality of life and overall patient satisfaction in patients with diabetes in Qatar. A new mobile application was specifically built for people with diabetes in Qatar with the help of the local expertise. We plan to conduct an open-label randomized control trial in which patients with diabetes will be randomized to the use of the diabetes application versus the current standard care. We hypothesize that the diabetes-specific mobile application will improve glycemic control, increase patient empowerment for self-management of diabetes and improve interaction between patients and health care providers

2. Abbreviations and Acronyms

List abbreviations, acronyms and terms of reference used in the protocol; provide definitions for each as needed

- App: mobile application
- HCP: health care provider
- HGH: Hamad General Hospital
- DM: diabetes mellitus
- T2DM: type 2 diabetes
- T1DM: type 1 diabetes
- GDM: gestational diabetes mellitus
- HbA1C: Hemoglobin A1c
- SMBG: serial monitoring of blood glucose
- POC: Proof of Concept
- QMI: Qatar Metabolic Institute

3. Introduction / Background*

In this section provide an in-depth background and introduction to justifying the nature, design and intent of the research. At the end the reader should have a clear idea of the research question, an understanding that it is original and relevant, and how this research will help fill the gap in knowledge.
This is NOT where the scientific activities and methods for the proposed research are described.

Diabetes Mellitus (DM) is a chronic disease characterized by an elevated level of blood glucose and carries the risk of acute and chronic complications. DM has a high prevalence across many nations especially within the Middle East (1). In Qatar, DM prevalence in the adult population is approximately 16.7%. DM management is a well-known complex process that requires both lifestyle change and effective pharmacologic treatment plans. To avoid DM complications, effective behavioral change, extensive education and promotion of appropriate self-management is key (1). As currently there is no cure for DM, self-management plays a vital role over the course of the patient's lifetime. Self-management includes measuring and recording blood glucose levels, exercising, maintaining a healthy diet, and regularly taking prescribed medications(2).

Self-management tools are developing fast. Data recording of blood glucose and lifestyle changes have progressed from writing them on a paper, to uploading them to computers, to recording them on mobile phones using traditional phone functions, and finally to using smartphone Apps(2). Mobile health is becoming one of the fastest growing areas of effective healthcare delivery in many countries with health education and awareness programs being increasingly recognized as the key players. Mobile healthcare (m-Health) can be defined as 'mobile computing, medical sensors, and communications technologies between healthcare providers and patients. The surge of m-Health systems in the last few years is due to the massive demand of such systems to alleviate and provide more efficient and effective healthcare delivery mechanisms especially for chronic disease management and self-care(3).

Many systematic reviews and meta-analyses proved that m-Health tools are effective in self-management in a wide range of areas both for disease-management and lifestyle changes in daily life(2). However, providing optimal care for patients with diabetes remains a challenge for healthcare systems and providers. Patients often encounter various barriers in adhering to self-management programs due to lack of knowledge and understanding of self-care activities, lack of individualized and coordinated care, inconvenient and costly education sessions, and poor patient-provider communication(4). Many of those barriers are due to cultural and societal factors, and consequently research is needed to identify which factors will arise in Qatar. Overall, mobile technologies offer new and exciting opportunities for addressing some of these challenges by enabling remote patient monitoring and delivery of clinical advice through a wide range of functions (e.g. text messaging, web browsing, email, and video)(4). In the case of diabetes management, m-Health might improve the accessibility, and ability of patients, to engage in treatment intensification (5).

Many different types of smartphone applications exist regarding T2DM self-management, such as "Easy Diabetes", "Diabetes Manager", "myDiabetes" and many others(2). Numerous characteristics of these Apps including increased accessibility to educational resources and self-management strategies, more frequent physical and emotional symptom tracking, and increased access to peer support are all main strengths in benefiting self-management of

patients(2). Focusing on high-quality systematic reviews that offered the most direct evidence, it has been demonstrated that on average, mobile phone-based interventions with clinical feedback improve glycemic control (HbA1c) compared to standard care or other non-mHealth approaches by as much as 0.8% for patients with type 2 diabetes and 0.3% for patients with type 1 diabetes, at least in the short-term (12 months)(4).

The recent studies on the use of newer mobile technologies for diabetes self-management have proven to be effective in improving HbA1c levels especially in patients with an HbA1c < 8%. The effectiveness of mobile health Apps is likely to be influenced by local culture and population mix. However, to date the effectiveness of this approach for Qatari patients is unknown. Mobile-phone/smartphone-based self-management Apps appear to have moderate benefit on glycemic control with a pooled effect on HbA1c reduction of -0.40% (-4.37 mmol/mol), indicating that the mHealth App intervention could improve glycemic conditions in patients with diabetes. This agrees with previous systematic reviews regarding self-management of diabetes(2).

Recently, Alotaibi and colleagues (1) have shown in a pilot study on 20 patients with T2DM randomized into control or intervention groups that mobile health technology significantly improves HbA1c levels among Saudi patients and improve their disease management. The mean HbA1c of the intervention group decreased from 8.8% to 7.9% at the end of the 6-month period. However, for the control group, the mean baseline HbA1c slightly increased from 8.6% to 8.7%. The study also showed a remarkable increase in the diabetes knowledge of the patients in the intervention group over the control group who followed the traditional methodology of patient monitoring. The mean baseline diabetes knowledge for the intervention group rose significantly from 46.2% to 61.1% in 6 months using an adapted Diabetes Knowledge questionnaire. The control group also showed slight increase from 43.7% to 46.1% (1).

Numerous Apps for DM management are readily available. However, there are no quality Apps in Arabic (14), with most Apps designed for high-income countries with different levels of health literacy than Qatar. The proposed App (Droobi) for our research has the advantage of being created in Qatar the local patient population, taking into account cultural adaptation and context.

Importantly, based on well-known quality criteria Droobi has been co-created taking into account patient, doctor and educator perspectives, identifying what is missing and what can be improved in care. It is aimed for Droobi to play a mediator role between physician, educator and patient, serving to fill the gap in current service provision, in an innovative, more efficient, and non-intrusive manner.

Keeping in mind the scarcity of data in the literature available for diabetes mobile Apps in Arabic, we believe this study will provide significant insight for the scientific community and shed light on an area gaining interest currently, which is promoting behavioral change, ultimately aiming to improve patient satisfaction, empowerment and clinical outcomes.

In conclusion, mobile health technologies can potentially be an effective and low-cost solution in improving the quality of life of patients with diabetes in the country considering the high level of prevalence and increasing economic burden of this disease. This study plans to investigate the impact of mobile health technology on DM self-management in Qatar.

4. Objectives *

In this section provide a clear statement of the primary and any secondary objectives of the study, include a clearly defined hypothesis and anticipated outcome.

Objective 1: App development and optimization. A proof of concept (POC) pilot shall be used to test the mobile App on a small group of patients to collect feedback to be used for App optimization aiming to improve its ease of use and functionality.

Objective 2: App effectiveness in diabetes management. We shall examine the hypothesis that the mobile App empowers patients with type 2 diabetes to manage their disease leading to improved glycemic control. Other outcomes of interest are diabetes self–care, and treatment outcomes using a randomized clinical trial (Qatar Diabetes Mobile Application Trial abbreviated as QDMAT).

5. Study Methodology *

In this section outline and describe in detail the intentions and actions of the study. The researcher should consider all aspects of the following and how each is applicable to the proposed research.

At minimum the following must be explained

- *Type and classification of study, comparisons and/or interventions. What is being studied or compared? If the research is a cohort study or survey then what are the exposures or predictors of interest?*
- *Setting and location of study, are there multiple sites?*
- *Sample size calculation or justification of numbers*
- *Details of the interventions (not procedures) involved in the research; what are you doing and who are you doing it to?*
- *Describe what data/samples (bio-specimens/information) will be collected at each time point and why*

  ***Specific details are required for treatment interventions and therapeutic treatments that involve drug(s), medical devices and clinical care. Are the risks to participants in the proposed research reasonably worth the anticipated benefits to clinical/health outcome?*

Objective 1: App development and optimization. Initial phases consisted of studying the current situation at the diabetes clinics at Hamad Medical Corporation (HMC) the largest medical provider in Qatar; reviewing with physicians, educators and patients the diabetes management issues with the current system; the workflow and bottlenecks;

what would they like changed; their interpretation of a mobile health solution for diabetes care. Members from the Qatar Metabolic Institute and Trio Investment worked together and developed the basic concept of a mobile App. The App will be refined and optimized using feedback from a small group of patients and healthcare professionals. Here we propose to do a Proof of Concept (POC) pilot on 30 patients to collect feedback regarding the functionality of the App to be used for App optimization before testing its effectiveness in DM management in Qatar.

The Proof of Concept (POC) pilot study
The main objective is collecting feedback from patient and health care professional to improve the app functionality before testing its effectiveness in diabetes management. Since one of the main benefits of the app is to help patients in relaying their blood sugar levels and adjusting their insulin doses accordingly, we plan in this pilot to select patients on insulin therapy regardless of their type of diabetes. Therefore, we plan to include a total of 30 patients on insulin therapy who have T2DM, T1DM; GDM and DM in pregnancy.
- here we are evaluating app usage amongst the 4 groups; the patient interaction; app usability; frequency of use; issues with the app; patient perceptions regarding the interaction with the healthcare professionals. This study will include qualitative and quantitative research methods such as interviews, focus groups, mobile app analytics, etc. in collaboration with HBKU.
- duration: 6 weeks - 3 months
- number of patients: 30
- setting: HGH outpatients and WH diabetes clinics

Objective 2: App effectiveness in diabetes management. We shall examine the hypothesis that the mobile app empowers patients to manage their disease leading to improved knowledge, skill and treatment outcomes. We plan to perform a randomized clinical trial (Qatar Diabetes Mobile Application Trial (QDMAT)) where patients receiving optimal care at the diabetes center are randomized to two groups, i) one using the App combined with the standard medical care ii) other using standard medical care alone.

The Qatar Diabetes Mobile Application Trial (QDMAT)
Population: Adult patients with T2DM on insulin therapy
Subjects with T2DM will be randomized into an intervention arm and standard care arm. Subjects in the intervention arm receive usual diabetes care in addition to the mobile App while subjects in the standard care will receive usual diabetes care only. Subjects

will be randomized using a computer-based software. Subjects will be stratified according to gender, age, level of HbA1c, diabetes duration and medications.

A diabetes population comparator group will be used to examine the natural progression of diabetes and its treatment outside the randomized controlled trial. This population with contextualize and determine the effectiveness of the trial arms compared to a non-randomized population.

Location: HMC diabetes clinics and Qatar Metabolic Institute (Building 311, Hamad Medical City) clinics and research unit
Sample size estimate:
We estimate that the use of the application will lead to a difference in HBA1C of -0.5% +/- 1% between the intervention arm and the standard care arm. To achieve an 80% power and a significance level of <0.05; 64 subjects should be recruited in each arm. Assuming a 40% loss of follow up, 90 subjects will be recruited in each arm. Sample size calculations were made using STATA 15 MP. For the population comparator group, we aim to select 200 patients identified through the diabetes registries at HMC and MoPH to examine the impact of intervention arms compared to a non-randomized group.
Duration: 12 months RCT with follow up via electronic medical records for up to 5 years

Trial Outcomes:
Primary Outcomes

- Difference in mean (change from baseline) HbA1C between the intervention arm and the standard care arm at 6 months.

Secondary Outcomes

- Difference in mean (change from baseline) HbA1C between the intervention arm and the standard care arm at 3 months
- Within subject changes in perceptions of diabetes self-management as assessed by diabetes self-management questionnaire (DSMQ) scores subsection glucose management and overall rating
- Within subject changes in attitudes towards disease assessed the proportion of subjects with diabetes distress scales scores consistent with moderate or high distress.
- Difference in number of recommended insulin dose adjustments per subject between App and usual care arm
- Difference in the number of reported hypoglycemic events per subject between the App and usual care arm.

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- Reduction in the time required to reach normoglycemia (in-range blood glucose readings) between the intervention and control groups.
- Differences in the number of clinical interactions per subjects with healthcare providers through the mobile App and through usual means in the standard care arm.
- Percent of missed clinical appointments in each arm.
- Changes in weight, blood pressure and lipids from baseline at 6 months

Exploratory outcomes

- Increased mobile Application usability and acceptance by
  - the system usability scale at 6 months
  - documentation of patients' experiences with the mobile Application
- Further analysis of patient characteristics in terms of responders and non-responders to the mobile intervention
- Reduction in hospital admissions

Population comparisons:
The trial arms will be compared to a comparator matched group identified via electronic medical records over the same period as the RCT and beyond. Only clinically captured data will be used.

Intervention
Subjects in both arms shall have regular access to their primary endocrinologist using the standards of care at the HMC National Diabetes Center clinics who shall manage their diabetes according to the current standards (Qatar Diabetes Guidelines; American Diabetes Association guidelines). In addition, subjects in the intervention arm shall utilize the mobile App in between their appointments to communicate with their health care team.

Data collection
- Patient medical background and history of diabetes at the start of the clinical trial
- Weight, Height, BMI
- Blood Pressure and heart rate
- Baseline HbA1c, complete blood count, lipid panel, urine albumin to creatinine ratio (ACR). comprehensive metabolic panel (CMP), TSH, ferritin, vitamin B12 and vitamin D levels
- HbA1c at 3-4 months and 6-7 months together with lipid panel, urine ACR, CMP, CBC and the above investigations if needed to be repeated.

-Review of patient following standards of diabetes care (retina, podiatry, dietetics, educators)

- Review of hospital admissions and hypoglycemia at each clinic visit

Questionnaires:

Two questionnaires will be conducted at baseline and 6 months for both the standard and intervention groups. An additional questionnaire, the system usability scale capturing the users' App experience will be conducted at the end of the trial for the intervention group

• Diabetes Distress Scale (DDS) developed in 2005 to assess the patient's psychosocial distress in diabetes. 17-item questionnaire measuring diabetes-specific distress in four domains: emotional burden, diabetes interpersonal distress, physician-related distress, and regimen-related distress (10)

• System Usability Scale widely used for testing usability of computing systems in the health domain (11)

• Diabetes Self-Management Questionnaire (DSM-Q): A 16 item questionnaire to assess self-care activities associated with glycemic control. Four subscales, Glucose Management (GM), Dietary Control (DC), Physical Activity (PA), and Health-Care Use (HU), as well as a Sum Scale (SS) as a global measure of self-care (12)

Questionnaires (10,11,12)

The questionnaires have all been tested and validated in English, with each questionnaire being related to a specific area of measurement.

- The questionnaires shall be translated to Arabic via the MRC translation services
- The Arabic translation validation will be performed by the research team internally.

Training

- The App has been designed to be simple to use, mimicking to the largest extent possible existing social media tools like WhatsApp, as our preliminary research shows high adoption of that technology in the target population. Patient training will take place with the educator and Trio team during the initial patient set up phase.
- Prior to the POC feasibility study the users will be offered a face-to-face training session in both English and Arabic for 30 minutes including a live demonstration or a video.

During the trial, which involves a larger number of participants, we will offer a one-to-one training session with the participant, displaying the mobile application and its key features in the patients preferred language. Live demonstration on the participants phone will be performed, and the participant is instructed to demonstrate and self-try the application in the presence of the team to ensure that they are able to use the application comfortably. The team ensures the participants training checklist is completed. In addition, we will provide a printed manual, which will also include advice for minimizing patient risk (e.g. no app is

substitute for medical advice, especially during medical emergencies, how to use the app and protect privacy).

- Similar training will be conducted for the educators and physicians involved in the intervention arm.
- These will be carried out by the Trio team involved in the study, together with the PIs facilitating interaction
- For any technical questions or concerns, the participants (both patients and healthcare professionals) will have available user support platform during the study duration in addition to a Droobi hotline number.

Please refer to Droobi's user guides online: https://www.droobihealth.com/user-guides

Additionally, refer to the patient, dietician, educator and physician training checklists

6. Study Population*

In this section describe the study population that is to be enrolled in the study; is the source of the research participants or data? Is it PRE-EXISTING data or will the proposed research be collecting NEW data or enrolling subjects? Indicate the quantity of participants or data sets needed to conduct the research.

- *If enrolling living human subjects, how and where are they going to be recruited from? How has privacy or confidentiality been addressed? Are they a member of a population that could be considered vulnerable or at risk to pressure to participate in research or at higher risk of harm from the research? For example, patients, children, pregnant women, economically disadvantaged, disabled, etc*
- *Explain how potential subjects are identified: What is the Inclusion/Exclusion criteria? i.e. Must the participant have a specific health condition or be healthy? For example have a condition such as asthma or diabetes to participate?*

Inclusion Criteria

- Adults with T2DM (more than 18 years of age and younger than 60) who are able to provide consent
- Arabic speaking and non-Arabic speaking T2DM patients, who can communicate in Arabic and or English language.
- Uncontrolled diabetes with HbA1c more than or equal to 8.5%
- T2DM on insulin with or without any other oral medication
- Subject must have a smart phone (either iOS (Apple) or android phone user) and must be interested in using a smart phone app.
- Subject must have no visual impairment.
- Minimal level of literacy (able to read and write in English or Arabic).

- To be able to communicate via chat with the mobile app team through the app as evidenced by at least weekly use of any of the social media such as WhatsApp, Viber, Facebook Messenger etc.
- Subject must be willing to utilize a mobile application for diabetes control

Exclusion Criteria

- Recent history (3 months) of stroke or Myocardial infarction.
- Patients with proliferating retinopathy
- Patients with an acute illness during the past 2 weeks.
- Patients who plan to be away for more than 3 months.
- Patients with CKD requiring dialysis.
- Hypoglycemia unawareness.
- More than one episode of severe hypoglycemia in the previous 6 months.
- Female patients who are planning for pregnancy in the coming 6 months.

Recruitment: from the HGH Diabetes clinics, diabetes educators and dietetics clinics, pharmacy lists, Diabetes Registry, and QMI clinics. Comparator group will be identified via existing electronic medical records.

Refer to QDMAT Study Manual pages 13-14

Additionally, in order to recruit more potential participants in the study, MRC approved media announcements regarding the study will be placed in the HMC social media pages including Facebook, Instagram and twitter.

Refer to QDMAT media ad_ Arabic and QDMAT media ad_English

7. Study procedures *

This is the most comprehensive part of the protocol, it outlines and describes in detail the processes and operations of the study, including logistics. And determines the compliance and oversight requirements of the proposed research such as ICH GCP & IRB.

In this section describe all the procedures that will be used to conduct the research and how they affect the participants enrolled in the research.

- *Study timelines: Expected duration of the study& start times, stages of the study such as screening, treatment phase, visit numbers, etc*
- *Is it a multi arm trial? For randomized studies; how are patients going to be randomized (a simple diagram showing treatment arms is often useful- attach file to protocol) Is randomization treatment blinded from subjects and/or research staff? If so why?*

- *Detail the interventions or treatments used, explain how they are delivered (if applicable) and who is going to deliver them? (Clinicians vs researcher staff) Standard of clinical care vs research activity (Therapeutic vs experimental or placebo)*

Provide a copy of any intended forms or diagrams as appendices to the protocol and list all on section 16 of this form.

Type, Timelines, Interventions

Proof of Concept (POC) Pilot

Patients: 30

Start: upon MRC approval projected January 2018

Duration: 6 weeks - 3 months

Screening: 2 weeks

Randomization: None

Interventions

- Initial visit by physician and educators for baseline characteristics and reviewing diabetic history

o HbA1c will be performed as well as kidney function

- Usage of mobile App education by research team

- Patients will be subscribed to the App and their profile will be created

- Enrolled patients will log in their blood sugar readings and communicate with the diabetes team (educators and physician) via the App

- Throughout the study; patient interaction and App usage will be tracked

- At each interaction with the research team; subjects will be asked for feedback and suggestions to improve the App using qualitative research methods.

- HbA1C will be performed again at the end of 3 months

Qatar Diabetes Mobile Application Trial (QDMAT)

Patients: 180; 90 cases; 90 controls

Start: August 2019

Duration: 12 months

Screening for eligibility: 2 – 3 months

Screening Visit

Potential participants obtained from physicians/educators/pharmacy lists/media ad are contacted over phone. The study is explained to them and they are briefly reviewed for inclusion/exclusion (on insulin therapy, have iPhone/android etc) and asked if they are willing to take part. They are then asked to sign a screening consent for giving blood and urine samples to complete their eligibility criteria. Once their blood and urine labs are completed and they satisfy the inclusion/exclusion criteria, they are called in for their initial (baseline) study visit.

Consent:

Initial visit for baseline characteristics of all subjects and reviewing inclusion/exclusion criteria and obtaining consent

Refer to the QDMAT Study Manual pages 15-16

Randomization:

Randomization will be done through a web-based randomization system accessed by study research personnel. The allocation sequence was provided by the online randomization service (www.sealedenvelope.com). The allocation is generated once participant eligibility criteria are entered into the platform by clinical research coordinators blinded to any allocation.

Interventions:

There will be 3 teams of health care professionals involved in this study

- The mobile App team: this team is formed of health care providers comprising of physician, diabetes educators and dieticians who shall provide feedback and coaching to patients through the App as designed using all clinical information available in the app
- The conventional clinic team: this team is formed of licensed health care providers (physician, educator and dietician) who shall provide clinical care according to the standards of care practiced at the National Diabetes Center. The mobile App health care provider team members may be part of the standard usual care team; according to clinic and provider availability.
- The data collection team: this team is formed of research assistants who shall assist in reviewing eligibility and obtaining consent. Additionally, they will be responsible for administering the questionnaires to all subjects and collecting the data at the beginning and end of the study duration (at time 0 and 6 months of the study)

Please refer to QDMAT Flowcharts

For all subjects:

The following shall be collected by the “Data Collection Team” at baseline, and 6 months

- Questionnaires regarding Diabetes Self-Management and Diabetes Distress

The quantity of blood collected in the study, is similar to that collected as standards of diabetes care and regular follow up

<u>One week prior to each clinic visit for ALL patients</u>

- Blood will be collected for HbA1c, CMP, CBC, Lipid profile, TSH, vitamin D, ferritin and vitamin B12
- Urine Albumin Creatinine ratio

The estimated amount of blood to be extracted for research purposes is 10ml

<u>At each clinic visit for ALL patients</u>

- Vital signs (BP, HR), weight, and records of any adverse events
- Record of current insulin dose as well as changes in medication regimens and insulin doses

Record of any medication side effects/adverse events

- Record of any hospital admissions
- Record of any hypoglycemia

For the subjects using the App (intervention group): The mobile App team shall do the following:

- Educate/train patients on App usage
- Patients will be subscribed to the App and their profile on the App will be created
- Subjects will log in their blood sugar readings and communicate with the mobile App team (educators and physician) via the App
- Additionally, patients will be placed on a diet and lifestyle plan as agreed upon by the patient and health care provider team, best suited towards the patient's needs
- Throughout the study, patient will receive notifications and advice on how to follow diet and lifestyle changes
- Throughout the study; patient interaction and App usage will be tracked
- Patients will additionally be interviewed by the research team together with Droobi to capture App experience at 3 months and 6 months

o Please refer to HMC patient interview questions

For the subjects not using the App (the standard of care group):

- At time 0, will be seen by the dietician and diabetes educators at HGH endocrine clinics as part of standard care

- The educators contact number and diabetes hotline number will be provided to the patients

o The diabetes hotline number is a new service provided to patients with diabetes at the National Diabetes Center to help communicate with the diabetes educators with questions relating to their diabetes management, medication adjustment such as dose titrations etc.

- Appointments thereafter with the educator and/or dietician will be decided and scheduled according to the individual subject needs, with a minimum visit every 3 months during the study period

For the comparator population, patients records will be identified via electronic medical records to match inclusion/exclusion criteria of RCT participants.

In this section describe the intended enrollment of people in the proposed research.
Will living human subjects be recruited, how many, how long will participants be expected to take part in the research? Is there follow up? When and for what?

Are there other limitations on the subject, such as pregnancy, medical, diet or concurrent research restrictions as a result of participating in this protocol?

Human Subjects

- For the POC pilot 30 patients will be recruited

o Expected duration: 6 weeks - 3 months

o Follow up at time 0 and 3 months as clinic visits to follow up HbA1c

- For the Clinical Trial 180 patients to be recruited; 90 intervention (cases) versus 90 standard of care (controls)

o Expected duration: 12 months

o Follow up at time 0, 3 months and 6 months for HbA1c and other blood and urine investigations and to complete questionnaires at time 0 and 6 months

- For the comparator population, 200 patients records will be identified via electronic medical records to match inclusion/exclusion criteria of RCT participants.

- Subjects must complete at least visit 0 and 6 months to be considered as study completers.
- Once completed the study duration, the mobile application for the intervention group will be deactivated and they will be returned to standard care i.e. directed to diabetes hotline in between their regular scheduled physician visits.
- It is intended to follow participants over a 5-year period beyond the completion of the trial to examine distal outcomes including glycaemia, blood pressure, lipids, medications, and key diabetes complications using subjects' electronic medical records.

In this section describe if and how the research will be obtaining informed consent from participants prior to enrollment and participation in the proposed research. Describe when, where and by whom the consent will be carried out by including how long subjects will have to decide if they want to participate?

- *How will the informed consent process, if applicable, be executed?*
- *Is there more than one type of informed consent form (ICF)? Languages? Request for Waiver? Etc.*

Provide a copy of intended forms as appendices to the protocol and list all on section 16 of this form.

Informed Consent

Screening informed consent will be obtained from the participants once they come in for their blood and urine investigations for the study. Participants will be informed that this is a screening consent and does not mean that they have been enrolled in the study. A follow up visit to explain their results and complete enrollment (if eligible) will be arranged.

Once the participant is deemed eligible for the study after reviewing labs and inclusion/ exclusion criteria, the details of the study are explained. Here the study details, what is required from the participant, benefits and risks are reviewed. After which, the consent is obtained.

Please refer to the Appendix QDMAT consent form
Additionally, refer to the QDMAT Study Manual pages 15-18

In this section describe the anticipated risks associated with participation in the research (i.e. illness, injury, death) In addition, indicate if these risks are different (higher or lower) than those associated with receiving standard clinical care or not participating in the research. For example, procedures for blood draws, MRIs, etc.

Risk
No anticipated serious adverse events from the enrollment in the study; the mobile Application will improve access to medical care; and hence no foreseen events. As for the usual care and intervention groups, they will be both provided with timely clinic visits every 3 months. The inclusion criteria comprise patients with uncontrolled diabetes. Thus, the patients (both arms; intervention and standard of care) may suffer from diabetes complications during their study enrollment as the natural course of the disease. [myocardial infarction, cerebrovascular accidents, diabetic retinopathy, nephropathy and diabetic foot].

All transmission from the mobile Application of health data will use encryption and other security mechanism to avoid any potential risk to privacy.

In this section describe what specimens or samples will be collected specifically for research, if the bio-specimen is from a sample taken from clinical care procedure (i.e. a blood sample taken for care, and the left over being used for research) or if the collection is ONLY for research and if specimens will be stored long-term and/or destroyed. Consider what happens to data/specimens if subject withdraws consent.

Bio-Specimens & Sample Collection
The samples collected are part of standards of routine diabetes care

HbA1c, CBC, Lipid Panel, CMP, TSH, ferritin, vitamin D and B12 and urine Alb/Cr ratio will be collected every 3 months for the study period duration.

In this section provide details on the outcome measures and the anticipated primary & secondary outcomes

Trial Outcomes
Primary outcomes

- Difference in mean HbA1C (change from baseline) between the intervention arm and the standard care arm at 6 months.

Secondary outcomes

- Difference in mean HbA1C (change from baseline) between the intervention arm and the standard care arm at 3 months
- Within subject changes in perceptions of diabetes self-management as assessed by diabetes self-management questionnaire (DSMQ) scores subsection glucose management and overall rating
- Within subject changes in attitudes towards disease assessed the proportion of subjects with diabetes distress scales cores consistent with moderate or high distress.
- Difference in number of recommended insulin dose adjustments per subject between app and usual care arm
- Difference in the number of reported hypoglycemic events per subject between the app and usual care arm.
- Reduction in the time required to reach normoglycemia between the intervention and control groups.
- Differences in the number of clinical interactions per subjects with healthcare providers through the mobile app and through usual means in the standard care arm.
- Percent of missed clinical appointments in each arm. Changes in weight, blood pressure and lipids from baseline at 6 months

Exploratory outcomes

- Increased mobile application usability and acceptance by
    - the system usability scale at 6 months
    - documentation of patients' experiences with the mobile application
- Further analysis of patient characteristics in terms of responders and non-responders to the mobile intervention
- Reduction in hospital admissions

Comparator population: We will examine the above measures in the comparator clinic population via electronic medical records.

Longer-term follow-up: It is intended to follow participants over a 5-year period beyond the completion of the trial to examine distal outcomes including glycemia, blood pressure, lipids, medications, and key diabetes complications.

In this section provide details on what data will be collected, how it will be collected, transcribed, transferred, and used. Consider who has access (shared), delegated rights and if the data can be correlated back to an individual participant. Is data collected directly from subjects or indirectly from public means? Will data be entered into a database? By who & how (using CRFs)?

Data Collection & Integrity

All personal data will be coded and all patients enrolled into the study will be given a unique and confidential subject ID only accessible to the research team. The unique IDs and data collected will be stored in the database in an encrypted format. The database that contains personal information of the patient will be kept separate from the database containing their health information. The only connection between the databases will be the Unique Identifier which again will be encrypted throughout the study and during data transmission.

The data entered by study participants will be directly sent over a secure line to the database for storage. There will be no third party involved in the transmission of data. The transmission of data from the mobile application to the server will include the use of JSON Web tokens. These tokens are used to validate the user.

In this section describe why a subject may be withdrawn from the study by the PI, what happens to the data or bio-specimens if a subject withdraws consent, and how complaints from participant's in research are handled

Subject Withdrawal/ Withdrawal of Consent

Taking part in the RCT is voluntary. Subjects may withdraw from the study at any time without their treatment or access to services being affected. Also, the PI may stop participation of subjects if they develop a condition that excludes them from the study. The data related to subjects who withdraw from the study shall be analyzed with an "intention to treat" analysis. Samples collected from subjects who withdraw their consent shall be discarded. Any complaint from a participant will be reviewed by the research team and will be addressed promptly

8. Data Management *

In this section describe specifically how data will be managed <u>after collection</u>, how is it secured, stored and destroyed. Consider who has access, delegated rights and ownership of the generated / used data; summarize if CRFs, questionnaires or other resources will be used to collect data and subject information. Provide a copy of intended forms as appendices to the protocol and list all on section 16 of this form including a data retention and destruction plan.

Data storage and security: All the data collected will be stored locally in Qatar at the MEEZA data centers. The data will be secured both at rest and during transmission. The data at rest will be encrypted at the file-based level (per-document, per-field) using AES-256 encryption protocol. The data during transmission will be secured using OpenSSL. The combination of encryption at rest with transport layer security along with access controls helps ensure compliance with the security and privacy standards including HIPAA.

Access controls: The data in the servers will be accessed remotely by the users using usernames and passwords. Once logged in, all the activity will be logged for each user. The logs will be encrypted. Access control list will provide users with the rights to access and perform functions using applications, programs. The authorized will only be able to access the minimum necessary information needed to perform job functions. The access control list will be managed by the Trio team. Anonymized data (without health data) about mobile application usage will be send to online services for analytics of usage patterns such as Google Analytics and Flurry.

9. Adverse Event Reporting*

In this section, provide a definition of anticipated adverse events that are related to the research, including a description of how SAEs will be assessed, tracked and reported; also provide a description of the stop rules for participation in the research.

Insulin titration is expected to occur more frequently in the intervention arm; hence we expect to potentially have more non-severe hypoglycemic episodes in this arm. This is a common adverse event that is part of the daily experience of patients on insulin and is seen in any insulin related studies.

Additionally, because of changes in the participant's medication regimens, they may face some medication side effects. Participants will be asked about medication side effects at each doctor visit.

However, if there are severe hypoglycemia/hyperglycemia, the App will provide instruction to seek emergency care.

For technical issues relating to the App for Drs, patients, educators Trio will provide a contact number and email address throughout the study period.

Refer to QDMAT Study Manual pages 22-23

10. Statistical Analysis*

In this section detail the analysis plan, how the primary and secondary outcomes will be analyzed, statistical methods to be used and who is going to carry out the analysis?
The data will be analyzed by the PI and research team with expert support from MRC.

Descriptive statistics will be used to summarize and determine the sample characteristics and distribution of patients' data. The normally distributed data and results will be reported with mean and standard deviation (SD) with corresponding 95% confidence interval (CI); the remaining results will be reported with median and inter-quartile range (IQR). Categorical data will be summarized using frequencies and proportions. Associations between two or more qualitative data variables will be assessed using Chi-square ($\chi 2$) test or Fisher Exact test as appropriate. Quantitative data between the two independent groups will be analyzed using unpaired t or Mann Whitney U test as appropriate.

Relationship between two quantitative variables will be examined using Pearson's or Spearman's correlation coefficients. Difference in mean change from baseline HbA1C between the intervention arm and the standard care arm at 3 and 6 months will be analyzed using repeated measure ANOVA method (followed by Bonferroni multiple comparison adjusted method), linear regression and analysis of covariance (ANCOVA) methods as appropriate. All analyses will follow the intention to treat analysis with last observation carried forward. Sensitivity analysis will be conducted using other approaches based on data available. Comparisons will be conducted between trial group and the observational cohort using the approaches described above.

Changes in perceptions of diabetes self-management (as assessed DSMQ) scores subsection glucose management and overall rating, changes in attitudes towards disease assessed the proportion of subjects with DDS scores will be analyzed using mixed liner regression models controlling potential factors and covariates possibly associated with both scores. Categorized DSMQ and DDS scores will be analyzed using logistic regression method and results will be presented and reported in odds ratio (OR) and associated 95% CI. For multivariate regression models, variables will be considered if statistical $P<0.10$ level in univariate analysis or if determined a priori to be clinically important. All P values presented will be two-tailed, and P values <0.05 will be considered as statistically significant. All Statistical analyses will be done using statistical packages SPSS 22.0 (SPSS Inc. Chicago, IL) and Epi-info (Centers for Disease Control and Prevention, Atlanta, GA) software.

11. Quality Assurance, Monitoring & Safety*

In this section briefly describe any plans or committees responsible for the review and monitoring of research conduct, data, quality, safety and performance outcomes. i.e. IRB, Ethics, Study Steering or Data Safety Monitoring Board? Will there be an interim analysis?

The study will be submitted to the HMC IRB for review and approval. The Endocrine Division has a weekly meeting devoted to discuss/review issues related to adverse reactions, side effects or concerns (ethical, data collection, quality, safety, outcome) raised or observed by subjects, coordinators or investigators. The group includes the Principal Investigators, research coordinators and research staff.

12. Ethical Issues & HSRP*

In this section provide a description of how human subjects' protections are in effect, if there are inducements for recruitment, what is the risk profile of research, known risks of research procedures (history) and which compliance entities will provide oversight for people enrolled in the proposed research..

The study will be conducted in accordance with conditions and requirements of IRB approval, the research protocol, and good clinical practice. The procedures and blood sampling are standard procedures and there are no additional risk factors for human subjects enrolled in this study as compared to any other human study.

13. Sponsor, Funding & Collaborator Information

Provide basic details of the lead sponsor and/or funding bodies, including name, and contact information, allocated number for the research, etc. For example QNRF

As relevant, include information on key collaborators, sub-contractors, etc to support feasibility and anticipated liability of research conduct for multi-center studies. Do not include financial specifics as this is handled through a different MRC process.

Trio Investment is a Qatar based technology investment company, its objective is to identify the digital intervention that will help to transform key target industries in MENA and create meaningful impact.

Trio Investment is a network of entrepreneurs, investors and innovators working at the intersection of healthcare and technology, analyzing digital disruption across the healthcare pathway and identify focused opportunities that have the highest value proposition to the healthcare sector.

14. Dissemination of Results and Publication policy

The protocol should specify not only dissemination of results in the scientific media, but also if results will be shared with the community and/ or the participants, and if dissemination to policy makers is intended.

Results from the current study will be summarized and reported annually to the Diabetes Division. Additionally, manuscripts will be prepared and submitted for publication. Study findings will be disseminated at appropriate conferences or symposia including Excellence in Diabetes Conference, American Diabetes Association annual meeting and other international, regional or local endocrinology and diabetes conferences through posters and invited talks. Furthermore, the results will be utilized by Trio in supporting their conclusions regarding the effectiveness of mobile products in improving the conditions of diabetic patients in Qatar. We will also make our findings available to our extended targeted audience including the general public in Qatar.

15. References

Cite the sources of all reference materials used to support the hypothesis so that a reader or reviewer can find them; this can be done using endnotes, footnotes and/or a bibliography.

1- Alotaibi MM, Istepanian R, Philip N. A mobile diabetes management and educational system for type-2 diabetes in Saudi Arabia (SAED). mHealth 2016; 2:33

2- Cui M, Wu X, Mao J, Wang X, Nie M (2016) T2DM Self-Management via Smartphone Applications: A Systemic Review and Meta-Analysis. PLoS ONE 11(11): e0166718

3- Seto E, Istepanian R, Cafazzo J, Logan A, Sungoor A (2009) UK and Canadian Perspectives of the Effectiveness of Mobile Diabetes Management Systems. 31st Annual International Conference of the IEEE EMBS – Minneapolis, MN, USA

4- Kitsiou S, Pare G, Jaana M, Gerber B (2017) Effectiveness of mHealth interventions for patients with diabetes: An overview of systematic reviews. PLoS ONE 12(3): e0173160

5- Istepanian RS, Zitouni K, Harry D, Moutosammy N, Sungoor A, Tang B, Earle KA. Evaluation of a mobile phone telemonitoring system for glycemic control in patients with diabetes. J Telemed Telecare. 2009;15(3):125-8.

6- RSH Istepanian et al. Mobile phone blood glucose monitoring. Journal of Telemedicine and Telecare 2009; 15:125-128

7- Ristau R, Yang J, White J. Evaluation and Evolution of Diabetes Mobile Applications: Key Factors for Health Care Professionals Seeking to Guide Patients. Diabetes Spectrum Vol. 26, Number 4, 2013

8- Bonoto et al. Efficacy of Mobile Apps to Support the Care of Patients with Diabetes Mellitus: A Systemic Review and Meta-analysis of Randomized Controlled Trials. JMIR Mhealth Uhealth 2017;5(3):e4

9 Alhuwail, Dari. "Diabetes Applications Smartphones." Nursing Informatics. 2016.for Arabic Speakers: A Critical Review of Available Apps for Android and iOS Operated

10. Polonsky WH et al. Assessing Psychosocial Distress in Diabetes

Diabetes Care Mar 2005, 28 (3) 626-631; DOI: 10.2337/diacare.28.3.626

11. Brooke, J.: SUS: A "Quick and Dirty" Usability Scale. In: Jordan, P.W., Thomas, B., Weerdmeester, B.A., McClelland (eds.) Usability Evaluation in Industry, pp. 189-194. Taylor & Francis, London (1996)

12.Schmitt A et al. The Diabetes Self-Management Questionnaire (DSMQ): development and evaluation of an instrument to assess diabetes self-care activities. Health and Quality of Life Outcomes 2013, 11: 138

16. Appendices*

An appendix is any attachment to this protocol or any other document that will be used to support the conduct of the research. Examples are case report forms, data collections sheets, informed consent forms.

List in this section all intended forms or resources that will be used in the conduct of research to collect data, interview people, recruit participants, etc. Provide a copy as an attachment to the protocol.

1. QDMAT Charts and workflows
2. QDMAT Informed Consent Form
3. QDMAT Screening Consent Form
4. QDMAT Data Collection Sheets
5. Study Questionnaires: DDS, DSMQ, Usability scale
6. Training checklists (Patient, Doctor, Dietician, Educator)
7. HMC Interview questions
8. QDMAT Study Manual
9. QDMAT media ads

Protocol Signature Page

I agree to conduct this research study in accordance with the design and specific provisions of this protocol and will only make changes in the protocol after notifying the required authorities.

Study Title:	Qatar Diabetes Mobile Application Trial (QDMAT)
Version Date:	25/04/2021
Principal Investigator (PI):	Dr Noor Nabeel M. Suleiman
PI Title, Department:	Consultant, Endocrine & Diabetes
Hospital:	Hamad General Hospital
PI Signature:	
Date of Signature:	