DIABETES TREATMENT IN RURAL GUATEMALA

A single group, pre-and post-test feasibility/pilot study of a smartphone application to assist community health workers in improving glycemic control in patients with type 2 diabetes in highland Guatemala.

Principal Investigator: Jim Svenson

This document is confidential.
No part of it may be transmitted, reproduced, published, or used by other persons without prior written authorization from the Sponsor or Principal Investigator.

PROTOCOL VERSION and AMENDMENTS

Protocol Version	Date	Change Initiated (Initials)	Brief description of protocol modification/actions requested, if any
Template V6	9/6/16	TNK	Input from IRB, OCT, MARCH, IND/IDE services, PIs
1.0	11/13/17	SMD	Initial submission
1.1	12/20/17	SMD	Updates on storage of study data (section 9.1)
1.2	12/21/17	SMD	Change to urgency of referral for vision problems, removed Alejandro Chavez from Key Personnel section
1.3	2/20/18	SMD	Changed hosting platform from Ona to CommCare

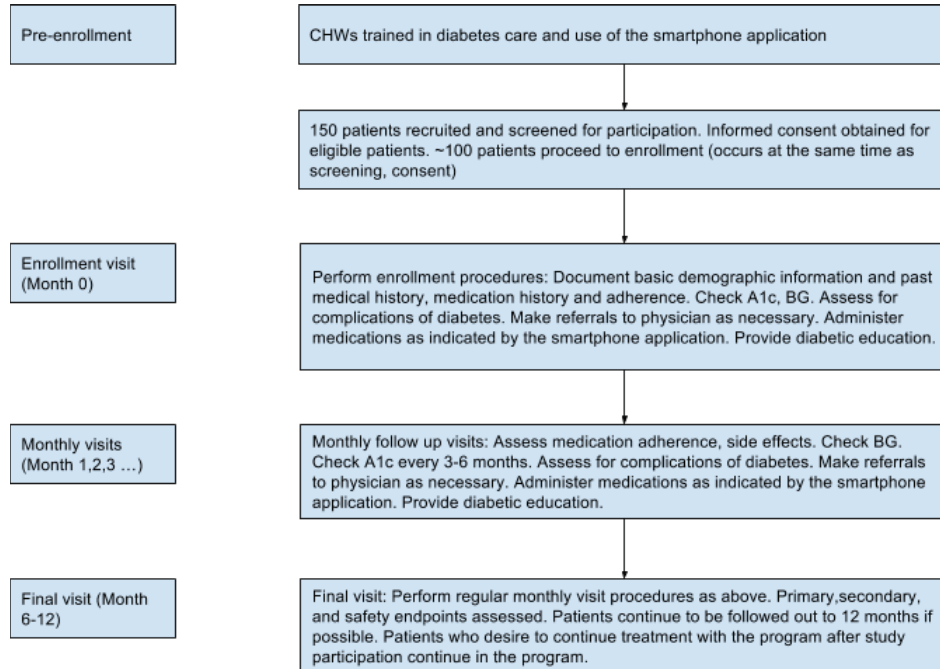|	
Funding Sponsor:	University of Wisconsin Global Health Institute 4270B Health Sciences Learning Center, 750 Highland Avenue, (608) 262-3862
Study Product:	Smartphone application for assisting community health workers with diabetes care in low resource areas
Protocol Number:	2017-0596 (IRB application number)
IND/IDE Number:	Not applicable
Participating sites:	San Lucas Mission, San Lucas Tolimán, Guatemala

2

List of Abbreviations

ACS	Acute coronary syndrome
AE	Adverse event
ANOVA	Analysis of covariance
ASCVD	Atherosclerotic cardiovascular disease
BP	Blood pressure
CAD	Coronary artery disease
CFR	Code of Federal regulations
CHW	Community health worker
CKD	Chronic kidney disease
CLIA	Clinical Laboratory Improvement Amendments
COPD	Chronic obstructive pulmonary disease
CRF	Case Report Form
CRO	Contract Research Organization
CVD	Cerebrovascular disease
DBP	Diastolic blood pressure
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
FBG	Fasting blood glucose
FDA	Food and Drug Administration
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH E6	International Conference on Harmonisation Guidance for Industry, Good Clinical Practice: Consolidated Guidance
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Investigational Review Board
ISO	International Organization for Standardization
LMICs	Low- and middle-income countries
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NIH IC	NIH Institute & Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
POC	Point-of-care
PPBG	Postprandial blood glucose
QA	Quality Assurance
QC	Quality Control
SBP	Systolic blood pressure
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

Version #: 1.0

SLM	San Lucas Mission
SLMH	San Lucas Mission Hospital
SMC	Safety Monitoring Committee

Study Summary

Title	Diabetes Treatment Algorithm for Minimally Trained Providers in Rural Guatemala
Short Title and Precis	Diabetes Treatment in Rural Guatemala. Implementation of a diabetes treatment program led by community health workers (CHWs) using a smartphone application to provide protocol-driven care.
Protocol Number	2017-0596
ClinicalTrials.gov number	NA
Phase	NA, implementation and feasibility study
Methodology	Single group, pre-and post-test feasibility/pilot study.
Study Duration	The expected duration of subject participation from enrollment to study completion (including follow up) is 12 months
Study Center(s)	Multi-center. Site will be the rural communities surrounding San Lucas Tolimán, Guatemala
Objectives	1. Implement a CHW-led diabetes program to improve diabetes care in the rural communities surrounding San Lucas Tolimán, Guatemala 2. Assess the efficacy of CHWs equipped with a smartphone application on improving glycemic control in this setting
Number of Subjects	100 to 150
Diagnosis	Type 2 diabetes mellitus
Main Inclusion Criteria	Adults 18 years and older with previously-diagnosed type 2 diabetes
Main Exclusion Criteria	Pregnancy, insulin dependency, type 1 diabetes
Study Product, Dose, Route, Regimen	Study uses a smartphone application to guide CHWs through treatment protocols, which was developed for the purposes of this study. Drugs used in the program are metformin, glibenclamide and aspirin.
FDA status of product	Drugs used are FDA approved
Statistical Methodology	Continuous variables will be assessed with paired t-tests. Categorical variables will be analyzed using the McNemar test for binary matched-pairs data.

Schematic of Study Design

Pre-enrollment	CHWs trained in diabetes care and use of the smartphone application

150 patients recruited and screened for participation. Informed consent obtained for eligible patients. ~100 patients proceed to enrollment (occurs at the same time as screening, consent)

Enrollment visit (Month 0)	Perform enrollment procedures: Document basic demographic information and past medical history, medication history and adherence. Check A1c, BG. Assess for complications of diabetes. Make referrals to physician as necessary. Administer medications as indicated by the smartphone application. Provide diabetic education.

Monthly visits (Month 1,2,3 …)	Monthly follow up visits: Assess medication adherence, side effects. Check BG. Check A1c every 3-6 months. Assess for complications of diabetes. Make referrals to physician as necessary. Administer medications as indicated by the smartphone application. Provide diabetic education.

Final visit (Month 6-12)	Final visit: Perform regular monthly visit procedures as above. Primary,secondary, and safety endpoints assessed. Patients continue to be followed out to 12 months if possible. Patients who desire to continue treatment with the program after study participation continue in the program.

Contents

Version #: 1.0

                                                                              8

9

Version #: 1.0

10

1   Key Roles

Following is a list of all personnel in key roles:

Jim Svenson, MD, Primary Investigator
University of Wisconsin-Madison School of Medicine and Public Health
800 University Bay Rd, Rm 349, Madison, WI 53705
608-215-3216
jes@medicine.wisc.edu

Sean Duffy, MD, Co-investigator
University of Wisconsin-Madison School of Medicine and Public Health
1102 S Park St, Madison, WI 53715
608-354-7930
sean.duffy@fammed.wisc.edu

Rafael Tun, MD, Site investigator
San Lucas Mission
La Parroquia, San Lucas Tolimán, Sololá, Guatemala
+502-7722-0899
dr.rafael.tun@gmail.com

Mark Kelly, MD Candidate 2019, Research Assistant
University of Wisconsin-Madison School of Medicine and Public Health
750 Highland Ave, Madison, WI 53726
608-338-8949
mmkelly2@wisc.edu

Kevin Wyne, MPAS, MSc, PA-C, Co-investigator
University of Wisconsin-Madison School of Medicine and Public Health
750 Highland Avenue, Room 1278, Madison, WI 53705
608-263-5620
kwyne@wisc.edu

2   Background and Introduction

2.1 Background and Rationale

The burden of chronic adult diseases is surging worldwide, particularly type 2 diabetes, the prevalence of which is expected to double by 2030. The diabetes epidemic will primarily impact developing countries, with 80% of adult cases occurring in low- and middle-income countries (LMICs) [1–4]. Because many LMICs currently face a shortage of health professionals, the increasing burden of noncommunicable diseases, like type 2 diabetes, will tax already strained health systems[5–8]. Furthermore, because many LMIC health care systems were developed to target acute illnesses and communicable disease, they are ill-prepared to treat and manage chronic adult disease[9,10]. The divergence between the growing burden of chronic disease and the development of the health systems necessary to treat these diseases indicate the potential for a grave health, economic, and human crisis in the following decades. The WHO has consequently demanded that physicians designs systems providing "Innovative Care for Chronic Conditions" to meet this challenge[4].

However, existing tools may provide a foundation for solutions to this growing crisis. Community Health Workers (CHWs, as known as health promoters) have become central to global health strategies since the Alma Ata Declaration of 1978, particularly in regions with physician shortages[11]. In recent years, CHWs have had notable success in targeting childhood disease, particularly malnutrition and diarrhea, and offer a growing variety of primary care services[12–15]. The success of these programs in providing consistent, sustainable care at the local level implies that longitudinal treatment for chronic adult diseases could be provided through parallel structures. While the treatment of chronic disease has become increasingly complex, the proliferation of smartphone and tablets across the globe have raised hopes that mobile health technology (mHealth) platforms can provide CHWs with algorithmic guidance on assessing and treating a broader set of diseases[8,16]. The potential use of mHealth is a burgeoning field of global health research[17]. The combination of CHWs and mHealth guidance may provide a solution to the rise of chronic disease in regions with physician shortages and weak health systems.

While many mHealth applications have been developed for Diabetes (over 1,000 are commercially available), only a small percentage (7.6%) are targeted to providers – and even fewer to providers in LMICs[18,19]. Instead, these tools most commonly serve as tools for patient self-management, patient education, and medication adherence. A handful of programs have utilized smartphone technology to connect remote patients to health care workers in LMICs as well as to provide clinical guidance to providers, but such programs have been minimal and publications have been process oriented[20,21]. In addition to improving diabetes care in our target population, our project also seeks to add to the evidence for this approach by designing an application-based algorithm that can assist CHWs in providing long-term diabetes care, titrating first- and second-line oral diabetes medications, and identifying dangerous diabetes complications in a setting of a lower middle-income country with a low physician density.

To test this delivery approach, we focused on developing a diabetes treatment program in San Lucas Tolimán, Guatemala. This program seeks to provide treatment to diabetics living in the group of 19 rural villages with a combined population of 17,000, which surround San Lucas. San Lucas is an ideal community for studying these topics because it is facing a heavy burden of untreated Type II Diabetes, has medical personnel with mHealth experience, and has a well-developed CHW program. This CHW program is sponsored by the San Lucas Mission (SLM), an NGO providing health services in the area and a University of Wisconsin and Stanford University partner organization. Local health workers describe the increase in Type II Diabetes as an epidemic and there are few systems in place to provide community members with diabetes screening or effective and consistent treatment. Startling regional data on Type II Diabetes supports this concern: in Guatemala, the prevalence of diabetes has been estimated at 9.1-9.4%, with over 40% of cases undiagnosed[22–24]. The prevalence of diabetes has doubled over the past 30 years[25]. Fortunately, San Lucas has already developed a strong CHW program, including a tablet-based mHealth application that targets early childhood malnutrition, through a collaboration between the San Lucas Mission and Stanford School of Medicine. This application has enhanced the successful malnutrition program, allowing CHWs to more easily identify and manage malnutrition and decreasing training requirements for CHWs[26]. Utilizing the existence of the CHW program infrastructure and the established mHealth platform, our project seeks to develop and implement a CHW-led diabetes treatment program in San Lucas that is assisted by a smartphone application.

In order to inform the development of the smartphone application and program protocols, we conducted a community needs assessment during the summer of 2016. Clinical data was used to provide a baseline estimate of diabetes prevalence and distribution in the communities as well as demographic risk factors. Interviews were conducted with local physicians, CHWs, and managers of the CHW system to understand current methods of diabetes treatment and define the limitations of these systems. Out of the 119 patients currently diagnosed with diabetes in the rural communities, 31 were interviewed to illuminate how the disease is currently diagnosed and treated, the effect the disease has on patient lifestyles, and patients' desired attributes for a diabetes treatment program. Finally, we visited local diabetes clinics to determine the current state of diabetes treatment, the availability of medications and resources, and the level of care provided to patients.

Key findings of the community needs assessment were as follows:

12

1. Patients with diabetes in the rural communities have poor access to quality diabetes care. Only 58% of patients are taking medication on a regular basis and only 13% have achieved good glycemic control
2. Outreach clinics run by CHWs are disorganized, undersupplied, sporadic, and ineffective
3. CHWs lack the experience and training to effectively titrate oral diabetes medications, assess for possible complications, and provide health education for patients
4. Patients lack basic diabetes knowledge, particularly regarding self-management

Utilizing the knowledge gained with this needs assessment, established treatment guidelines for diabetes, and the expertise of SLM medical director Dr. Rafael Tun and the coordinators the SLM CHW program, we developed protocols for the diabetes program, including a smartphone application to allow for algorithmic management. This process was iterative and collaborative and involved our local partners at every step.

In February and March, we trained a group of 10 CHWs, including 5 CHW coordinators (who have more clinical experience and take on a supervisory and training role for less-experienced CHWs) in the basics of diabetes management, program protocols, and the use of the smartphone application we had developed. With close physician supervision, we then beta-tested the use of the application with a small group of patients. Based on this experience, we have further refined the application and program protocols. We now endeavor to implement this program on a wide scale in the San Lucas area to both improve access to care for patients with diabetes and to establish the efficacy, feasibility, and safety of CHW-led, smartphone application-guided diabetes treatment.

CHW training, program protocols, and the algorithmic approaches facilitated by the smartphone application will be described in more detail in the relevant sections of this protocol and its appendices. An overview of study activities is as follows:

● We will train additional CHWs in basic diabetes care, use of point-of-care (POC) testing technology, and use of the smartphone application that will guide their management of patients with diabetes.
● CHWs will recruit patients with diabetes in the rural villages outside of San Lucas to participate in the program.
● At the enrollment visit, CHWs will use the smartphone application to screen patients for appropriate inclusion in the program, establish glycemic targets, assess current glycemic control with hemoglobin A1c and blood glucose, measure height, weight, blood pressure, and waist circumference, assess for the presence of diabetes complications (diabetic ulcers, angina, diabetic eye disease), administer oral medications (metformin and/or glyburide, known locally by its alternate name glibenclamide) based on a medication dosing algorithm, and provide diabetes self-management education.
● CHWs will meet with patients on a monthly basis to assess medication adherence and for adverse effects, glycemic control (with blood glucose), screen for diabetic complications, refill medications with titration as needed (if experiencing medication adverse effects or blood glucose is significantly above or below treatment goals), and provide further diabetes education. Again, these activities will be guided by the smartphone application. Every 3 months, the monthly visit will also include A1c measurement for a more definitive measurement of diabetes control and to allow for titration of medications. Patients who are identified as having complications or who are not meeting treatment goals despite maximal dosing of metformin and glibenclamide allowed by the algorithm will be referred to SLM medical director Dr. Rafael Tun for definitive management.
● After all visits, including enrollment and monthly visits, Dr. Tun, in addition to the study investigators, will review data for all patients seen, including treatment recommendations made by the application and carried out by the CHWs, and make any changes to the treatment plan as needed based on his clinical judgement.
● Mean hemoglobin A1c and proportion of patients meeting treatment goals (primary endpoints) will be assessed at 6 months and compared to baseline, in addition to a number of secondary endpoints and safety measures as described in the relevant sections of this protocol. If possible, patients will also be followed out to 12 months with reassessment of primary and secondary endpoints.

- SLM hopes to continue this rural diabetes treatment program indefinitely, with the results of this study informing a quality improvement process to ensure the provision of high quality care.

A potentially controversial aspect of this program is that CHWs will be making metformin and glibenclamide dose adjustments based on an algorithmic protocol, with physician oversight occurring in a retrospective fashion. However, this approach has been used safely and effectively for chronic disease management in LMIC. For example, a validation study of the WHO CVD-Risk Management Package in India found that frontline health workers following a treatment algorithm for hypertension made the same decision as a physician with regarding to prescribing a thiazide diuretic 88-97% of the time[27]. Additionally, a diabetes treatment program in rural Guatemala working with indigenous patients, a population analogous to our target population, successfully utilized protocol-based care carried out by nurses to safely improve glycemic control and other treatment parameters[28].

We believe that the novel aspect of our intervention, the use of a smartphone application to guide treatment decisions, improves on these protocol-driven approaches in several ways. The use of a mobile computer-based algorithm as opposed to a paper algorithm allows for greater complexity and the incorporation of additional factors relevant to patient safety, such as the patient's current dose of medication, medication adherence, and medication side effects, in order to provide more specific recommendations. In this way, it decreases the cognitive burden placed on CHWs and the potential for human error. Rather than having to follow a complicated paper flowchart, CHWs will input information into the smartphone application, which will process the data and present the CHW with a concrete recommendation. Additionally, a computer-based system allows for easier review by the supervising physician and auditing and analysis of both program process measures and outcomes.

While CHWs will be acting on recommendations from the smartphone application without direct physician supervision at that moment, they will in essence be acting on "standing orders" from the physician because the treatment algorithms were designed by physicians and approved by the SLM medical director. CHWs will also be able to obtain point-of-care treatment recommendations from the medical director via telephone if there are questions about application recommendations or if a situation arises that falls outside the scope of the protocols.

2.2 Hypothesis

We hypothesize that the implementation of a CHW-led diabetes program utilizing algorithmic guidance from a smartphone application in the rural communities surrounding San Lucas Tolimán will lead to an improvement in glycemic control among the diabetic patients enrolled in the program.

2.3 Study Agent

In this study, we will be using a smartphone application that we developed to guide CHWs through the clinical assessment of patients with diabetes including collection of demographic data and past medical history, assessment of medication history, adherence, and adverse effects, measurement of glycemic control, screening for complications, medication administration and titration, and patient counseling. The application uses the CommCare platform by Dimagi and will be run on password-protected and encrypted Android smartphones. This application is based on web forms, which allow for skip logic questions and algorithmic processing of data. The application can be used offline. When internet access is available, collected data is uploaded to a secure server. The specific protocols and algorithms programmed into this application are described in further detail in the relevant sections of this protocol and its appendices.

We will use the following medications in our study (all FDA approved and being used for approved indications):

- Metformin HCl regular-release tablets 850 mg[29]
  - Description: Oral biguanide antidiabetic medication. First line medication for type 2 diabetes and used as monotherapy or in combination with other medications. Low risk of lactic acidosis

Deleted: consists of Enketo

Deleted: utilize Excel-based programing to

Deleted: These forms run in a smartphone browser and

Deleted: In our case, we are using password-protected Android smartphones with the Google Chrome mobile browser.

Version #: 1.0

- - Pharmacology: Decreases hepatic glucose production and increases insulin sensitivity. Not metabolized hepatically. Excreted largely intact by the kidney. Elimination half-life 17.6 hours

- Glibenclamide (glyburide) regular-release tablets 5 mg[30]
  - Description: Oral 2nd generation sulfonylurea antidiabetic medication. 2nd line treatment for type 2 diabetes
  - Pharmacology: Stimulates insulin release from pancreatic islet cells. May also cause reduction in hepatic glucose production and increase insulin sensitivity with prolonged use. Metabolized completely by the liver to 2 weakly active metabolites. Excreted in urine and feces. Terminal elimination half-life is 10 hours and duration of action is 18-24 hours

- Aspirin (acetylsalicylic acid) 81 mg tablet[31]
  - Description: Oral salicylate with analgesic, anti-inflammatory, and antithrombotic effects. Used for the treatment of ACS, ischemic stroke and primary and secondary prevention of ASCVD.
  - Pharmacology: Inhibits cyclooxygenase (COX) and thus decreases thromboxane A2, leading to decreased vasoconstriction and platelet inhibition. Metabolized rapidly by the liver to salicylic acid, which has a half-life of 3-10 hours depending on dose. Excreted in the urine.

FDA drug inserts for these medications have been uploaded to the ARROW application

2.4 Summary of Relevant Preclinical Data

No available research

2.5 Summary of Clinical Data

No available research

2.6 Dose Rationale

The standard doses for metformin and glibenclamide used in our program are as follows:

- Metformin: 850 mg, 1500 mg, or 2550 mg per day (850 mg dosed once, twice, or three times daily, respectively)
- Glibenclamide: 2.5 mg, 5 mg, or 10 mg one time daily

In accordance with diabetes treatment guidelines[32–34], metformin is the first line medication for all patients in the program and is continued in all patients as long as it is tolerated and there are no contraindications. The standard starting dose of metformin in our protocol is 1700 mg (850 mg twice daily) as 1500 - 2000 mg is thought to be the usual effective dose range[35,36].

Also in accordance with ADA and AACE guidelines, patients with initial or repeat A1c ≥9% are placed on dual therapy with metformin and glibenclamide. For patients who are initially started on metformin alone and whose A1c is <9%, glibenclamide is added if they are not meeting glycemic targets despite maximum daily dose of metformin (2550 mg). Though the maximum dose of glibenclamide is 20 mg, most of the hypoglycemic effect of glibenclamide is thought to come at the initial 2.5 mg dose and doses above 10 mg per day are not thought to provide significant additional benefit[37]. For this reason, the maximal dose of glibenclamide used in our program is 10 mg per day.

Glibenclamide does carry a higher risk of hypoglycemia compared to newer sulfonylureas such as glimepiride and glipizide. However, glibenclamide was selected for use in this program because other sulfonylureas are either not readily available in Guatemala or are prohibitively expensive compared to glibenclamide. In addition, though glibenclamide carries a higher hypoglycemia risk than other sulfonylureas, the risk of serious

15

hypoglycemia (requiring the assistance of another person or hospitalization) is still low, with reported occurrence in only 0.5% of patients in a meta-analysis of sulfonylurea studies[38].

The application will recommend aspirin for patients with a history of ischemic stroke and CAD to prevent recurrent events and for patients with possible ACS, as long as contraindications are not present. The dose used for ASCVD prevention is 81 mg per day, which is in accordance with current consensus guidelines[39,40]. The dosage used for treatment of possible ACS is 324 mg, also in accordance with current consensus guidelines[41,42].

2.7 Potential Risk and Benefits to Subjects

2.7.1 Known Potential Risks

Immediate risks
- The potential immediate risks include the risks of taking metformin, glibenclamide, or aspirin, medications which have been in use for decades and have well-established safety and side-effect profiles.
  - Metformin: The most common side effect of metformin is gastrointestinal distress (e.g. dyspepsia, nausea, vomiting, diarrhea). This usually improves with time and most patients can tolerate these side effects, with only 5% of patients discontinuing the drug completely because of them[36]. The most serious reported adverse effect of metformin is lactic acidosis. However, the incidence of this has been found repeatedly to be exceedingly low. In fact, a 2010 Cochrane review found no cases of lactic acidosis over 70,490 patient-years of metformin use, even when patients with some renal impairment were included[43]. Finally, metformin can cause vitamin B12 deficiency with long term use
  - Glibenclamide: The primary potential adverse effect of glibenclamide is hypoglycemia. The proportion of patients taking glibenclamide who will suffer an episode of severe hypoglycemia (requiring the assistance of another for treatment and/or hospitalization) is estimated to be 0.5%[38]
  - Aspirin: Significant potential adverse effects of aspirin include gastrointestinal toxicity, hemorrhage, renal toxicity, and hypersensitivity reactions
- Risk of errors in medication administration or recommendations due to user error or application malfunction
- Discomfort with finger sticks for blood glucose and hemoglobin A1c measurements

Long-range risks
- Complications of medication adverse effects (e.g. anemia from metformin or aspirin use, renal insufficiency as a related to aspirin use)

Reproductive risks: **Pregnant women are excluded from the diabetes treatment program**. However, it is possible that a woman of reproductive age could enroll without knowledge of current pregnancy or prior to becoming pregnant. Metformin is a class B drug in pregnancy (generally considered to be safe) and both metformin and glibenclamide have been used in the treatment of gestational diabetes, so their use would not be expected to engender risks other than those already described for the general population. In addition to the risks described above, which apply to a pregnant woman, aspirin also carries potential fetal risks of mortality, intrauterine growth retardation, salicylate intoxication, bleeding abnormalities, and neonatal acidosis. However, low dose aspirin, which is used in this program for the prevention of ASCVD in selected patients, is increasingly recommended for a number of different indications during pregnancy, including prevention of preeclampsia and continuation of aspirin therapy for prevention of stroke[40].

The risks of using these medications and the use of the application are justified by the fact that the patients in rural villages whom we are targeting would not otherwise have access to any consistent diabetes care. Not only this, but the care they do receive is often discontinuous and fragmented and the dose of medication or even which medication (glibenclamide or metformin) a patient receives depends on medication supply and the

Version #: 1.0

whim of the untrained health promoter or pharmacist. In this way, we anticipate that the risks of application-guided care will be less than the status quo.

We anticipate that our approach could also be adapted to resource-limited settings around the world, with the potential to extend diabetes and other chronic disease care to patients who do not currently have access to this care due to critical shortages in health system workforce capacity. The knowledge gained by this and subsequent studies to advance this cause warrants the potential risks.

Of the medications we will be utilizing, glibenclamide likely has the highest potential for harm. We did consider using other sulfonylureas which are thought to have a lower risk of hypoglycemia. However, as mentioned in section 2.6, alternate sulfonylureas are not reliably available in Guatemala and/or are prohibitively expensive. In addition, glibenclamide is one of the most widely-used sulfonylureas (and antidiabetic medications in general) worldwide[44]. Thus, the use of glibenclamide in this study may make our approach more generalizable.

We also considered the timing of implementation for dosing changes recommended by the application: in real-time during the visit with retrospective approval by the physician supervisor within 1-2 days or subsequent to physician approval of application recommendations. We ultimately decided that the logistics of requiring physician approval of application recommendations prior to dispensing medications would be prohibitively complicated and would likely lead to patients going without medications for significant periods of time, possibly leading to complications. In essence, the physician has "pre-approved" the medication changes because these are made according to an algorithm designed and tested by physicians and approved by the San Lucas Mission medical director. Additionally, CHWs will be able to consult their coordinator and/or the medical director via telephone at the point of care if there are any questions about medication dosing or other recommendations given by the application.

2.7.2   Protection Against Risks

The risks of side effects from medications will be mitigated by several mechanisms:
- As decreased renal function increases the risk of adverse effects of metformin and glibenclamide, renal function testing will be required prior to administration of medications for patients with a history of kidney disease and recommended for patients with hypertension and/or duration of diabetes of 10 years or greater. Glibenclamide and metformin will not be used for patients with eGFR <30 mL/min.
- Patients will be asked about adverse effects of metformin monthly. Patients who are taking glibenclamide will also be asked about hypoglycemia symptoms and medication will be down-titrated if these symptoms are present
- Patients above the age of 65 will have a less stringent treatment goal of A1c ≤8%, in accordance with ADA guidelines[32].
- Medication will only be up-titrated at 1 month checks when blood glucose is significantly above glycemic goals: FBG >180 mg/dL or PPBG >300 for patients below age 65 and FBG >200 mg/dL or PPBG >300 for patients 65 or older or with multiple comorbidities
- For aspirin use, patients will be asked about history of aspirin allergy in potentially emergent situations (when patient presenting with chest pain that could represent ACS) and aspirin will not be administered to patients with history of allergy. In non-emergent situations, patients will be asked both about history of allergy and signs of GI bleeding (blood in stool or black and tarry stools) prior to dispensing aspirin.

The risks of POC finger stick testing will be minimized by CHW training emphasizing sterile technique and standard precautions.

The risks posed by application malfunction or incorrect use will be mitigated by an intensive alpha testing process (systematically testing each possible scenario prior to implementation with patients to ensure correct

recommendations are given in every case), training of CHWs and physician oversight of application treatment recommendations and CHW decisions regarding medication administration and referrals.

Exit criteria for the study includes the following:
- Patient with eGFR <30 mL/min will be unable to safely take metformin or glibenclamide and thus will be excluded from the program. These patients will be referred to San Lucas Mission Hospital (SLMH) for consultation with Dr. Rafael Tun regarding alternate medication therapy.
- Women who are found to be pregnant during the study
- Patients who require insulin or additional medication other than metformin or glibenclamide for diabetes control

Patients with mild adverse effects, such as gastrointestinal upset from metformin or mild hypoglycemia or hypoglycemia symptoms on glibenclamide will have their medication adjusted according to the titration algorithms used by the application. Patients who are unable to tolerate metformin or glibenclamide due to adverse effects will be referred to Dr. Rafael Tun for assessment and further treatment recommendations. Patients with more severe adverse effects, such as severe hypoglycemia (defined as resulting in alteration in mental status and requiring assistance from a CHW) or hypoglycemia not responsive to initial measures in the field will be transferred to SLMH via ambulance for further care.

The program will pay the costs related to ambulance transfer to SLMH and the cost of treatment for medication adverse effects. Patients may incur costs from treatment for other complications of diabetes that fall outside the scope of the program, though this care is highly subsidized through the SLMH.

2.7.3   Potential Benefits to the Subjects

The primary potential benefit to patients is improved control of diabetes and avoidance of complications and premature death from this disease. Patients will also receive free medications and diabetes-related tests (blood glucose, A1c, and renal function testing if needed) while they are participating in the study. In addition, monthly visits will be an opportunity for patients to socialize and form supportive relationships with other patients with diabetes in their communities, which may contribute to an improvement in overall health and wellbeing.

3 Study Objectives and Purpose
- Primary Objective: Implement a CHW-led diabetes program to improve diabetes care in the rural communities surrounding San Lucas Tolimán, Guatemala
- Primary Objective: To assess the efficacy of CHWs equipped with a smartphone application on improving glycemic control in patients living in rural communities in Guatemala
- Secondary Objective: To assess the ability of CHWs equipped with a smartphone application to identify potential complications of diabetes in patients living in rural communities in Guatemala
- Secondary Objective: To assess the safety of diabetes medication titration by CHWs equipped with a smartphone application

4 Study Design and Endpoints

4.1 General Design

Design: This study is a single group, pre-and post-test feasibility/pilot study

The expected duration of subject participation from enrollment to study completion (including follow up) is 12 months

Version #: 1.0

Summary of trial periods:
- Enrollment: Months 0-6 (enrollment will be rolling)
- Safety analyses will occur on a monthly basis during the trial (evaluation of data from monthly visits)
- Evaluation of endpoints will first occur at 6 months post enrollment (6-12 months after study initiation for most participants). Participants will be followed up to 12 months post enrollment (12-18 months after study initiation for most participants) if possible based on program logistics and funding. Endpoints would again be assessed at that time

4.1.1 Primary Study Endpoints

The primary endpoints will be hemoglobin A1c at 6 months and 12 months post-enrollment. This will be analyzed and reported in two ways:
- Mean hemoglobin A1c in the study group compared to mean value at baseline
- Percentage of patients meeting treatment goal for hemoglobin A1c compared to this percentage at baseline. Treatment goal will be A1c ≤7 for most patients, A1c ≤8 for patients age 65 or older or who have 2 or more comorbidities, or other individualized goal for select patients as determined by the medical director (Dr. Rafael Tun)

4.1.2 Secondary Study Endpoints

- Mean A1c and proportion of patients at goal at 3 months and 9 months.
- Mean FBG at 6 and 12 months compared to baseline value
- Mean BMI at 6 and 12 months compared to baseline
- Mean waist circumference at 6 and 12 months compared to baseline
- Mean blood pressure at 6 and 12 months compared to baseline
- Number and percentage of patients identified as potentially having the following complications:
  - Angina
  - Foot ulcers
  - Ophthalmologic complications
  - Hypertension
- Percentage of patients successfully completing referrals for potential complications
- Number of patients referred for poor glycemic control or intolerance of diabetic medications and percentage of these patients who complete referral
- Prevalence of adverse effects of metformin and hypoglycemia symptoms throughout the study
- Patient medication adherence throughout the study and at 6 and 12 months compared to baseline
- CHW compliance with medication recommendations provided by the application (proportion of visits)

4.1.3 Primary Safety Endpoints

- Documented hypoglycemia (blood glucose <70 mg/dL)
- Hypoglycemia requiring emergency transport to the hospital and/or hospitalization
- Instances in which the application provided an incorrect recommendation
- Patient death

5 Study Subjects – Enrollment and Withdrawal

5.1 Subject Population

Subjects will include adults 18 years of age and older and will be recruited from the 19 rural villages surrounding San Lucas Tolimán, Guatemala. Treatment of children with diabetes entails greater complexity and is beyond the scope of this program. Though there are no enrollment restrictions based on race or ethnicity, the majority of the people living in these villages are from the Kaqchikel ethnic group, an indigenous Mayan people of the midwestern highlands of Guatemala.

19

5.2 Inclusion Criteria

Inclusion Criteria
1   Willing to provide written informed consent
2   Willing to comply with all study procedures and be available for the duration of the study
3   Male or female, at least 18 years of age
4   Prior diagnosis of type 2 diabetes
5   Resident of one of the rural communities served by the CHW network of San Lucas Tolimán

5.3 Exclusion Criteria

Exclusion Criteria
1.   Type 1 diabetes
2.   Women who are pregnant
3.   Current use of insulin
4.   Renal insufficiency (eGRF <30 mL/min/1.73 m$^{2)}$
5.   Unable to provide informed consent

5.4 Subject Screening for Recruitment

5.4.1 Subject Identification

Potential subjects will be identified by CHWs from their prior knowledge of individuals with diabetes in their communities. We also anticipate that study participation will be bolstered by word of mouth communication between patients in the communities. Patients may also be identified during mobile medical clinics run by visiting medical volunteers.

5.4.2 Recruitment and Retention Strategies

Potential participants will be contacted in person by CHWs. At that time, the health promoter will ask if they would like to participate in the study. We anticipate that more than women than men will enroll in the study based on prior experience of the CHWs in other health promotion programs. Men's availability is often less than women's because of their occupations (agricultural work with long and inflexible hours, long commutes or residential work in population centers). The communities we are working in are ethnically homogenous, so recruitment of minorities is not relevant. We anticipate recruiting around 150 patients.

5.5 Vulnerable Populations

TABLE 1: Vulnerable populations included and excluded from this study:

Include	Exclude	Vulnerable Population Type
	X	Adults unable to consent
	X	Individuals who are not yet adults (e.g. infants, children, teenagers)
	X	Wards of the State (e.g. foster children)
	X	Pregnant women
	X	Prisoners

20

Version #: 1.0

5.5.1 Subject Capacity

We anticipate that all subjects will have the capacity to provide informed consent. Patients who are not able to consent will not be included in the study.

5.5.2 Subject/Representative Comprehension

CHWs will use the "teach back" method [45] to assess subject comprehension of the potential risks and benefits of study participation.

5.6 Informed Consent

The PI will be responsible for ensuring that valid consent is obtained and documented for all subjects unless the IRB waives the requirement for documentation of informed consent for all or part of the study

5.6.1 Process of Consent

CHWs will obtain consent from each subject. The consent will be obtained during CHW visit for health care, either at the patient's residence or the clinical meeting site for their community. Consent forms will be translated into Spanish by Dr. Duffy, who is fluent in Guatemalan Spanish and has been certified to see Spanish-speaking patients independently by UW Interpreter Services. Consent discussion will primarily occur in Spanish. Most patients speak Spanish and Kaqchikel, a Mayan language, so some part of the consent discussion may occur in Kaqchikel as all CHWs are bilingual Spanish and Kaqchikel speaking. Most CHWs and patients are not literate in Kaqchikel, only Spanish, so the consent form will not be translated into Kaqchikel.

The amount of time given for the consent discussion will take approximately ten minutes but may last as long as necessary to ensure patient understanding of the study. The participant will be given as much time as needed to make a decision. All staff will undergo project specific training that includes methods of obtaining consent. These methods include thorough explanation of the study, risks and benefits of participation, emphasis of voluntary participation and withdrawal at any time, assurance that non-participation will not affect health care and provision of adequate time for independent decision.

Consent will be documented on paper forms, which will be stored in a locked receptacle either at SLMH or at the CHW headquarters in the village of Quixaya.

5.6.2 Consent Form (see [templates](#) for UW-Madison)
See in ARROW

5.6.3 HIPAA
Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 ([HIPAA](#)). Attached/submitted as part of our application is a signed subject authorization form that includes:

- The collection of the following protected health information (PHI)
    - Identifying information: name, date of birth, community
    - Past medical history and current medical problems
    - Your treatment for diabetes
    - Measurements: height, weight, waist circumference, vital signs
    - Lab results, including blood glucose and hemoglobin A1c
    - Information about symptoms and medical problems related to diabetes

21

- Access of this information by CHWs to provide diabetes care and carry out the program, SLMH Medical Director Dr. Rafael Tun to provide supervision of CHWs and oversight of treatment decisions, by the study investigators to supervise the study and analyze program efficacy and study results, and by the IRB for study monitoring and supervision.
- The patient can revoke their authorization if they decide to withdraw from the study

5.6.4 Revoking Consent

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

5.6.5 Costs to the Subject

The cost of study medications used in the program, POC and other lab testing and supplies, CHW labor costs, emergency transport of patients to SLMH as needed, and treatment of adverse effects from study medication (e.g. hypoglycemia) will be covered by funding from a Global Health Seed Grant from the UW Global Health Institute. In general, care provided at SLMH is free or very low cost, but patients may be responsible for the cost of care provided outside of the study protocols (payment for this care will not come from study grant funding).

5.6.6 Payment for Participation

Patients will receive free diabetes care through the study program, including medications, testing, emergency transportation to SLMH, and treatment of medication adverse effects as needed. There will be no additional compensation.

5.7 Early Withdrawal of Subjects

5.7.1 Premature termination of study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the PI or co-investigator to the IRB. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:
- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the IRB.

5.7.2 When and How to Withdraw Subjects

Subjects may be withdrawn from the study in the following scenarios:
- Subject consent withdrawal

22

Version #: 1.0

- Subject becomes pregnant
- Subject unable to take metformin or glibenclamide due to adverse effects or development of severe renal dysfunction (eGFR <30mL/min/173 m^2)
- Subject requires insulin or other alternative treatment for diabetes
- Clinical discretion of the site medical director, Dr. Tun

When subjects are withdrawn from the study, they will be promptly referred to Dr. Rafael Tun at SLMH for continuing diabetes and other appropriate medical care.

5.7.3   Data Collection and Follow-up for Withdrawn Subjects

Data collected prior to withdrawal will be included in the study.

6   Study Agent

6.1   Description and Formulation

In this study, we will be using a smartphone application which we designed to guide CHWs through the clinical assessment of patients with diabetes including collection of demographic data and past medical history, assessment of medication history, adherence, and adverse effects, measurement of glycemic control, screening for complications, medication administration and titration, and patient counseling. This application will run in the web-browser of an Android smartphone. This application is IDE exempt.

The medications we will be using are as follows:
- Metformin HCl regular-release 850 mg tablets
- Glibenclamide (glyburide) regular-release 5 mg tablets
- Aspirin 81 mg tablets

6.2   Packaging

Metformin and glibenclamide come in blister packages of 10 tablets each. Aspirin comes in a bottle.

6.3   Preparation, Administration and Storage of Study Drug

No preparation of the study drugs is necessary. They will be stored in a storage locker at the CHW headquarters in Quixaya, San Lucas Tolimán, Guatemala.

6.4   Route of Administration

All medications are administered by mouth. Patients will be treated with at least one of the three medications during the entire duration of the study and their participation in the diabetes treatment program (so, at least 6 months), aside from patients who may be observed off of medication to see if their diabetes is diet-controlled. Whether a patient is taking one of these medications or not depends on their individual characteristics, including glycemic control and targets, experience of side effects, and medication adherence, as described by the treatment protocols outlined below and in the appendices.

6.5   Starting Dose and Dose Escalation Schedule

Metformin will be started at 850 mg once daily and increased to the target dose of 1700 mg after 2 weeks. If not meeting treatment goals after ≥1 month, metformin can be increased to 2550 mg. Patients who are unable to tolerate the 1700 mg dose will take the 850 mg dose.

Glibenclamide will be used for patients who are unable to tolerate metformin, in addition to metformin if A1c ≥9, or if glycemic goals not met despite maximal dose of metformin. Dosing will start at 2.5 mg once per day. If glycemic goals are not met after ≥1 month, dose will be escalated to 5 mg once per day and then 10 mg once per day as needed.

Aspirin will be dosed at 81 mg once per day for secondary prevention in eligible patients with history of MI or stroke or patients who have new chest pain and are awaiting medical workup for possible CAD. Patients with high risk chest pain and possible ACS will be treated with aspirin 324 mg (four 81 mg tablets) once while awaiting emergency transport to SLMH.

Please consult Appendix 8, Appendix 10, and Appendix 11 for further information on medication titration protocols

6.6 Dose Adjustments/Modifications/Delays

See 6.5 above and relevant appendices

6.7 Prior and Concomitant Therapy/ Standard of Care

Some patients may already be taking metformin and/or glibenclamide prior to enrollment. Their doses will be adjusted based on glycemic goals, current control, medication adherence, and medication side effects. Patients may require additional medication therapy or other treatment for complications of diabetes or other health problems while they are participating in the study. The only medication that would preclude them from further participation in the study would be if they needed to start insulin for uncontrolled diabetes or emergence of a contraindication to metformin or glibenclamide.

6.8 Randomization and Blinding of Study Drug

This section is not necessary as this study is not a randomized or blinded trial.

6.9 Receiving, Storage, Dispensing and Return or Disposal of Study Agent

Table 2: Study Agent information at a glance:

Name	Source	Storage	Dispensing	Disposal
Metformin 850 mg tab	Drogueria Americana	CHW headquarters	CHWs	NA
Glibenclamide 5 mg tab	NeoEthicals	" "	" "	NA
Aspirin 81 mg tab	Drogueria Americana or NeoEthicals	" "	" "	NA

6.9.1 Receipt of Drug Supplies

Metformin, glibenclamide, and aspirin will be obtained from Drogueria Americana and NeoEthicals, S.A., two reputable pharmaceutical distributors operating in Guatemala City with whom SLM has worked for some time.

An inventory will be performed and a drug receipt log filled out and signed by the person accepting the shipment. The designated study staff will count and verify that the shipment contains all the items noted in the shipment inventory.

Version #: 1.0

6.9.2 Storage

Storage of medications will occur in a storage locker in the CHWs' headquarters in Quixaya. As such, they will not be exposed to sunlight or extremes of temperature. In the temperate climate of highland Guatemala, temperatures will not routinely vary from the 68-77 degree F storage temperature range and excursions would not exceed the 59 to 86 degrees F recommended for these medications[29–31]

6.9.3 Dispensing

Medications will be dispensed to each patient at monthly visits by CHWs as guided by the diabetes smartphone application. Adherence to medication will be assessed at each monthly visit by standardized patient report (see Appendix 3 for more information on how adherence assessment).

6.9.4 Return or Disposal

Unused medication at the end of the study will remain with the SLM CHW program to be used by patients continuing in SLM's diabetes treatment program.

7 Study Procedures

7.1 LABS

All patients will have POC HbA1c testing performed at baseline and every 3 months. The ADA does recommend individualization of A1c testing, advising quarterly checks in patients not meeting glycemic goals and at least twice yearly in those meeting treatment goals[32]. While we do intend to implement individualized testing in the diabetes program after the study period, testing will be every 3 months for all patients during the study period to allow for more uniform evaluation of program efficacy at the predetermined times of endpoint analysis (6 and 12 months for primary endpoints).

A1c testing will be performed with A1CNow®+ (PTS Diagnostics) POC capillary blood analyzers. This analyzer has been granted a CLIA waiver and has been certified by the National Glycohemoglobin Standardization Program (NGSP)[46].

Capillary blood glucose measurements will be conducted at baseline and monthly using the Bayer Contour® POC system. This is also CLIA-waived and has been validated in comparisons with plasma/serum glucose analyzers.

Both aforementioned POC testing systems are designed to be used by laypeople and patients without medical training, making them very appropriate for use by frontline health workers, as in our study.

Testing of serum creatinine will be checked at baseline for all patients with prior history of chronic kidney disease prior to administration of metformin or glibenclamide. Baseline creatinine will also be strongly recommended for patients with hypertension (defined as either taking antihypertensives or baseline BP ≥140/90) and/or duration since diagnosis of diabetes of 10 years or more. Serum creatinine will be checked at SLMH and reviewed by the medical director, who will then determine patient eligibility for metformin and/or glibenclamide therapy based on calculated eGFR.

Ideally, serum creatinine would be tested in all patients at baseline and prior to administration of metformin and glibenclamide. However, this is not performed routinely for diabetic patients in the San Lucas area due to the expense and availability of travel. Requiring testing for all patients prior to administration would likely severely restrict participation as it is likely many patients would not travel to San Lucas to have necessary testing done and subsequently be lost to follow up. For this reason, we have adopted a risk-factor based targeted testing strategy for checking renal function.

7.2 Established Standard of Care:

The current standard of care in the rural communities around San Lucas Tolimán is not consistent. There is a clinic based at SLMH in San Lucas Tolimán, which sees a group of ~100 patients, usually on a monthly basis. These patients are by and large from the city itself, as it is very difficult for patients from the rural communities to spare the time and expense to travel to San Lucas. This clinic is run by the two supervisors of the CHW program, who have significant experience in working with patients with diabetes and can titrate metformin and glibenclamide if blood glucose is persistently elevated. SLMH CHWs also hold clinics 3 of the 19 rural communities. However, supplies of medications and testing supplies are inconsistent and thus patients are administered medications based more on which medication and dosage is available rather than based on clinical judgement and patient condition. The CHWs staffing these rural clinics are unable to titrate diabetes medications in response to persistent hyperglycemia or adverse effects. Services at all of these clinics are limited to measurement of vital signs, blood glucose (when supplies available), dispensing of metformin and glibenclamide, counseling on diet and lifestyle, and referral to SLMH medical director Dr. Rafael Tun if complications are suspected based on CHW clinical judgement. No further laboratory testing or other assessment is routinely performed.

7.3 Study Visits

7.4.1   Screening/Baseline:

Training of CHWs
While not an element of direct patient care, an essential part of the diabetes program will be the training of CHWs prior to enrollment of patients. CHWs undergo a 6 week training program emphasizing health education and identification of patients who require definitive medical care. Many also have experience in using a mobile application to track and treat children with chronic malnutrition. However, many lack specific training on the management and complications of diabetes. We have designed training to fill in these gaps in diabetes-specific knowledge and to teach CHWs how to use the smartphone application and POC testing devices. We will also instruct CHWs on human subjects research ethics and the process of obtaining informed consent, as they will act as collaborating investigators.

Training will consist of the following elements (allotted times are approximate):
- Didactic sessions focusing on the basics of diabetes pathophysiology, lifestyle and medication management, and complications - 8 hours total. The PowerPoint presentation that will used for these session has been uploaded to ARROW in the Supplemental Information section.
- Didactic session on human subjects research protections and informed consent - 2 hours. We will use adapted CITI training that was developed by researchers from Marywood University on a prior research project performed with the SLM CHWs. These researchers have given us permission to use these materials, which are available in English and Spanish. As many of the CHWs have already reviewed this material, the reuse of this resource will have the added benefit of reinforcing their prior learning. The training documents are uploaded in the ARROW application.
- Practical workshop on the use of POC testing devices (A1CNow®+ and Contour® devices), measurement of blood pressure and pulse using the ReliOn™ BP200 automatic blood pressure cuff, body temperature using a digital thermometer, and anthropometric measurements (weight, height, waist circumference) - 4 hours
- Hands-on practice with the application with trainers taking on the role of patients to simulate patient encounters - 8 hours

Training will be conducted by study investigators with the assistance of CHW program coordinators, who have already gone through such training in order to carry out beta testing of the application with a small group of patients. We anticipate training approximately 30 CHWs for the diabetes program. As the program matures, the CHW coordinators will gradually take over more responsibility for CHW training to ensure local ownership and sustainability of the program (a "train the trainers" model).

26

For the first several months after completion of the training program, CHWs will be paired with one of the CHW coordinators while seeing patients for continued clinical mentorship and guidance.

Enrollment Visit
Patients will be screened for study eligibility on the same day of potential enrollment. If they are eligible, informed consent will be obtained and the CHW will proceed with enrollment and initial treatment of the patient with the guidance of the enrollment module of the smartphone application. The enrollment visit will consist of the following elements:

- Screening questions (Appendix 1) - Determine if patient is eligible to participate in the study. Done with verbal consent. If eligible, written and verbal consent obtained for full study participation and CHW proceeds to the next step.

- Collection of demographic information and relevant past medical history (Appendix 1) - This information facilitates the creation of a patient database and clinical registry, determines the patient's glycemic goal and if they need renal function testing prior to initiation of medications, and informs a decision about chronic aspirin therapy for secondary ASCVD prevention (Appendix 2). Glycemic goals are generally consistent with ADA guidelines[32] and are determined as follows:

  - Patients <65 years old with <2 comorbidities (CAD, CVD, COPD, CKD, cancer)
    - A1c goal ≤7%
    - FBG 80-130 mg/dL
    - PPBG <180 mg/dL
  - Patients ≥65 years old or <65 years old and with ≥2 comorbidities (as listed above)
    - A1c goal ≤8%
    - FBG 90-150
    - PPBG <200 mg/dL

- Medication history, adherence and side effects (Appendix 3) - This information factors into the confirmation of diabetes with A1c testing (for example, if a patient is not taking any medications and their A1c is 5.2, they may not have diabetes) and provides information for the application to determine starting medication for each patient. Information about whether a patient is taking medication for hypertension will also factor into whether renal function testing is recommended prior to initiating medication treatment.

- Glycemic testing, vital signs, and other anthropometric data - Fasting status, defined as no caloric intake for the past 8 hours, is determined. Blood glucose and hemoglobin A1c are collected for each patient. If hypoglycemia or severe hyperglycemia are identified at this stage, the application initiates management protocols (Appendix 4 and Appendix 5). CHWs also measure blood pressure, pulse (also collected by the automatic BP cuff), height, weight, and waist circumference. Hypotension or hypertension are addressed according to the protocol described in Appendix 12

- Screening for possible complications of diabetes (Appendix 6) - The application guides CHWs through an assessment for possible complications of diabetes, including diabetic foot ulcers, angina, and diabetic eye disease.

- Recommendations for referrals (Appendix 7) - Based on information collected and entered by the CHW, the application will make recommendations regarding the need for a referral to SLMH and evaluation the medical director Dr. Tun. Referral recommendations are classified as emergent (recommended immediate transport), urgent (evaluation by physician within 1-2 days), or routine (evaluation by physician within 1-2 weeks). CHWs are prompted by the application to immediately arrange for referral and transport for emergent conditions (e.g. current chest pain suspicious for angina) as soon as these conditions are identified. The recommendation for referral in these cases is a "hard stop" and the CHW will not be able to proceed with application questions until the emergent situation is addressed and

27

definitive care arranged. These recommendations for referrals are consistent with the WHO protocol for diabetes management in low-resource settings[47]

- Medication recommendations and counseling - Based on medication history, A1c, and glycemic goal, the application uses an algorithm to determine a recommended medication regimen for the patient, including the amount of medication to dispense (Appendix 8). The application provides information on how to take the medication and how to avoid adverse effects, which the CHW discusses with the patient (Appendix 9). The CHW then uses the "teach-back" method to ensure that the patient understands how to take their medication. The CHW will also provide patient education on diabetes self-management, including diet, physical activity, and foot care, with the assistance of demonstration materials developed for the program (uploaded to ARROW application in the Supplemental Information section).

Physician Oversight

Within 1-2 days of the enrollment visit and every subsequent visit, patient data from the smartphone application will be uploaded to a secure online database viewable to the supervising physician, Dr. Tun. Within 1 week of each visit, Dr. Tun will review the visit summary for each patient and either approve the current treatment or recommend changes to the treatment, including changes to the patient's glycemic target as necessary. Also during that 1 week timeframe, any changes recommended by Dr. Tun will be communicated to the patient through the health promoter coordinators and/or the health promoter who saw the patient.

If CHWs have questions regarding patient care while conducting a patient visit, they will contact one of the CHW coordinators and or Dr. Tun via telephone for advice on how to proceed.

7.4.2   Follow up:

Acceptable Window for Study Visits (including weekends)

Visit	Window	Activities
Monthly follow up visits	+/- 1 week	● Assessment of the following: ○ Medication adherence and tolerance ○ Glycemic control with blood glucose ○ Presence of diabetes complications ● Refill of medications, with titration of dosage as needed ● Diabetic education
Month 3 visit	+/- 1 week	Same as for monthly visit with the exception that A1c is checked (if indicated) in addition to blood glucose and is used for medication titration

Monthly Visits
CHWs will meet with patients once per month to follow up on adherence and tolerance to medications, assess glycemic control, assess for complications of diabetes, refill medications (with dosing adjustments as needed for side effects, non-adherence or poor glycemic control), and provide diabetic education. These monthly visits will be facilitated by the smartphone application monthly protocol. This protocol mirrors the enrollment protocol as described above, with the following exceptions:

- Basic demographic information and medical history are not reassessed. This information is carried forward from the enrollment visit
- Blood glucose alone is collected. A1c is not collected unless it was recommended to be done the month prior and was not collected at that time
- Algorithms for medication adjustments are based on blood glucose, preferencing fasting glucose over postprandial glucose (Appendix 10)

Month 3 Visit

Version #: 1.0

At every 3rd monthly visit, starting with the visit 3 months after enrollment, A1c will be assessed. When A1c is checked, the month 3 medication titration algorithm (Appendix 11), is used rather than the monthly titration algorithm, which uses blood glucose. This protocol also considers the current glucose measurement to account for cases in which glycemic control may have improved significantly in the past month due to medication or lifestyle changes, but A1c may still be above goal due to earlier hyperglycemia. For example, if a patient with A1c goal of 7 has an A1c of 7.5, but FBG of 105, the application will recommend that the patient continues with the current medication dosing rather than recommending a dose increase. Other than checking A1c and using the A1c-based algorithm as indicated, the procedures performed at the month 3 visit are identical to those of the monthly visit.

7.4.3 Unscheduled:

The CHWs live in the same communities as the patients they will be serving. As such, we recognize that patients may come to them with concerns outside of the structure of monthly visits as described above. We have designed an additional module for the smartphone application that guides the CHWs through an assessment for hypoglycemia or severe hyperglycemia and possible complications of diabetes. This module uses the same relevant protocols from the enrollment and monthly visits (see Appendix 4, Appendix 5, Appendix 6, Appendix 12). If a patient or CHW has a concern outside of the scope of these protocols, the CHW will contact a CHW coordinator and/or the medical director Dr. Tun for guidance.

7.4.4 Final Study Visit

All patients will be followed until at least 6 months post enrollment. Safety monitoring will occur on a continuous basis during the study and an interim analysis of efficacy will occur at the 6 month point. If permitted based on funding and personnel availability and the ability and desire of our local partners in Guatemala, patients will be continued to be followed out to 12 months post enrollment.

This study is based around the implementation of a program that the San Lucas Mission intends to continue indefinitely. Thus, patients who participated in this study will have the opportunity to continue their treatment through the CHW-led diabetes program. The study will inform a quality improvement process for this program and work to ensure program sustainability.

8 Study Analysis

8.1 Sample Size Determination

For this study, we plan to recruit approximately 150 patients based on the known population of diabetics in the rural communities surrounding San Lucas Tolimán. Of these, we hope to enroll at least 100 patients in the study. Using these numbers, statistical power was calculated using the UCSF online sample size calculators [48] for a one-group before-after study. The following parameters were used for calculation:

- $\alpha = 0.050$
- $\beta = 0.200$
- SD for outcome = 2.4 (this was the reported pretreatment SD for A1c for a population of 174 indigenous diabetics upon enrollment in a diabetes treatment program in rural Guatemala)
- Within-subject A1c correlation coefficient (r_{within}) of 0.928 (this is based on an analysis conducted to determine the accuracy and precision of the A1CNow®+ testing device[49], which we are using in our study)
- Sample size = 100

With this sample size, we will have adequate power to detect an effect size as small as 0.257% A1c and should easily be able to detect more clinically significant differences of 1% A1c or more.

Another primary outcome will be the proportion of patients meeting treatment goals vs this proportion at baseline. Using the above website, the same parameters for α and β, sample size of 100, and a baseline proportion of patients meeting treatment goals of 13% (this is based on a needs assessment that we conducted as part of this project), we would have 80% power to detect a proportion of 30.2% of patients with good glycemic control (OR 2.896 compared to baseline).

8.2 Statistical Methods

The primary endpoints will be hemoglobin A1c at 6 months and 12 months post-enrollment. This will be analyzed and reported in two ways:
- Mean hemoglobin A1c in the study group compared to mean value at baseline
- Percentage of patients meeting treatment goal for hemoglobin A1c compared to this percentage at baseline. Treatment goal will be A1c ≤7 for most patients, A1c ≤8 for patients age 65 or older or who have 2 or more comorbidities, or other individualized goal for select patients as determined by the medical director (Dr. Rafael Tun)

Secondary endpoints and analyses will include:
- Mean A1c and proportion of patients at goal at 3 months and 9 months.
- Mean FBG at 6 and 12 months compared to baseline value
- Mean BMI at 6 and 12 months compared to baseline
- Mean waist circumference at 6 and 12 months compared to baseline
- Mean blood pressure at 6 and 12 months compared to baseline
- Number and percentage of patients identified as potentially having the following complications:
    - Ischemic chest pain
    - Foot ulcers
    - Ophthalmologic complications
    - Hypertension
- Percentage of patients successfully completing referrals for potential complications
- Number and percentage of patients referred for poor glycemic control or intolerance of diabetic medications and percentage of these patients who complete referral
- Prevalence of adverse effects of metformin and hypoglycemia symptoms throughout the study
- Patient medication adherence throughout the study and at 6 and 12 months compared to baseline (proportion patient reporting each level of adherence)
- CHW compliance with medication recommendations provided by the application (proportion of visits)

Differences in continuous variables (e.g. mean A1c) will be analyzed using paired, 2-tailed t tests. Differences in categorical values (e.g. percentage of patients meeting treatment goal for A1c) will be analyzed using the McNemar test for binary matched-pairs data.

8.3 Subject Population(s) for Analysis

There will be no randomization and there is only one group, so all patients enrolled will be analyzed to the extent of their participation. Analyses will be as described above in section 8.2. Planned subgroup analyses include patients with A1c less than or equal to treatment goal at baseline, patients above treatment goal at baseline, and patients with A1c ≥9 at baseline.

8.4 Planned Interim Analysis:

Initial analysis of primary endpoints and safety endpoints will occur at 3 months post enrollment to determine if any significant changes are needed to treatment protocols.

Version #: 1.0

9 Data Collection, Handling and Record Keeping

9.1 Data Confidentiality

A service known as CommCare is being used to collect data. Whenever data is transmitted between one of the servers CommCare uses and the Android application, it is sent using HTTPS. Here are the standards incorporated:

- Encrypted server-client connections using HTTPS
- All access to the cloud infrastructure is protected behind a firewall and require unique VPN access permissions
- Data is transferred through channels monitored by intrusion monitoring systems
- Encrypted at-rest database and encrypted database backups every night
- Security management meets ISO 27001, PCI-DSS, SOC1, SOC2, SOC3, and HIPAA standards

The devices used to collect data are encrypted Android smartphones. The CommCare mobile application itself is password protected and data collected by the application is encrypted (AES 256-Bit Symmetric Encyption, fully HIPAA compliant). These are only connected to the internet when data is being uploaded via a WIFI connection. Currently the devices are only being used by the health promoters the days of the diabetes checks, which is usually just 2 or 3 days per month. As soon as all the checks have been completed the devices are returned to the health promoter main building where the data is sent using a WIFI connection and then erased from the device.

The data is stored with other hospital system data used in monitoring an infant nutrition program in a HIPAA compliant server (see above). This data essentially constitutes an aspect of the patient's medical record at the San Lucas Mission Hospital. Persons with access to this database will include SLM medical director Dr. Tun, the coordinators of the CHW program, Alejandro Chavez (onsite data manager and software engineer), Dr. Svenson (the PI), and Dr. Duffy (co-investigator).

Any hard copies of study data will be stored in locked filing cabinets at CHW headquarters in Quixaya and/or San Lucas Mission Hospital. When not in use, smartphones will be stored in a locked cabinet at CHW headquarters in Quixaya.

Data used for analysis of study outcomes will be extracted from this secure online medical record and stored on a secure UW Health (DFMCH) server in a password-protected Access database and/or password-protected Excel files. Data may also be sent to UW Health email using the Stanford University secure email service, which is HIPAA compliant. This data will not be de-identified. This data will be shared securely with IRB personnel as needed for study monitoring.

9.1.1 Confidentiality of Subject Records

By signing the protocol, the Investigator agrees that an IRB representative may consult and/or copy study documents in order to verify CRF data. By signing the consent form, the subject agrees to this process. If study documents will be photocopied during the process of verifying CRF information, the subject will be identified by unique code only and full names and similar identifying information (such as medical record number or social security number) will be masked.

The Clinical Site Investigators will ensure that the identity of subjects will be protected. All study records will be maintained in a secure fashion with access limited to essential study personnel only. All study documents submitted to the Coordinating Center will have identifiers removed other than dates of birth and service and subjects will be identified with a study-specific identification number only. The Clinical Site Investigators will maintain, in a secure location, an enrollment log that includes subject identifying information and links subjects to their study-specific identification number.

31

9.2 Data Capture

9.2.1   Source Documents

The primary source documents used for this study will be the electronic forms generated by the diabetes smartphone application, which contain all clinical data entered by CHWs during enrollment and monthly visits. For patients who are referred to San Lucas Mission Hospital for emergency care or other reasons germane to the diabetes program, paper medical records generated by these encounters will also be evaluated.

9.2.2   Case Report Forms

Case report forms will be based on the electronic forms generated by the diabetes smartphone application.

9.2.2.1   Missing Data

The smartphone application will assist in ensuring complete data entry in that most fields are required before the CHW can proceed to the next section of the visit and most data is entered through the use of radio buttons, pre-populated list options, and parameter-limited text boxes. Retention and follow up of patients will be enhanced by visiting patients who miss monthly group visits at their homes. Only patients who completed follow up to each relevant time point (e.g. 6 months, 12 months) will be included in these analyses.

9.2.3   Data Collection Tools

We will not be using UW institutional data collection tools.

9.3   Data Management

Data constituting patients' medical records will be stored in a secure database as noted in section 9.1. Data used for research purposes will be derived from this clinical database and managed by Dr. Duffy. This will be stored on a secure UW Health server in password-protected files.

9.4   Data Monitoring

The smartphone application used to carry out the protocols of the study and collect data has built-in consistency and range checks. Alejandro Chavez will upload patient data to the secure database after each round of patient visits and maintain the database. Site medical director Dr. Tun will review patient data for clinical supervision on a monthly basis, as will Dr. Duffy for safety and outcome monitoring. Dr. Duffy will meet with Alejandro Chavez at least every 2 weeks via Skype and as needed via email. Alejandro is in contact with Dr. Tun and the CHW coordinators on a daily basis. Dr. Duffy will also meet with Dr. Tun and the CHW coordinators via Skype as needed.

9.5   Records Retention

Records will be kept for at least 7 years following the study

9.6   Specimen Banking

Not applicable

10 Assessment of Safety

10.1   Specifications of Safety Parameters

Version #: 1.0

- Documented hypoglycemia (blood glucose <70 mg/dL)
- Hypoglycemia requiring emergency transport to the hospital and/or hospitalization
- Instances in which the application provided an incorrect recommendation
- Patient death

10.1.1 Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

For the purposes of this study, known and non-serious adverse effects of medications used in the study - metformin, glibenclamide, and aspirin - which have been used for decades and have well-established safety profiles, will not be considered adverse events. Examples of such non-serious adverse effects include gastrointestinal side effects of metformin and hypoglycemia symptoms associated with glibenclamide (without documented hypoglycemia).

10.1.2 Definition of Serious Adverse Events (SAE)

An adverse program effect will include any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, the diabetes treatment program, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with the program that relates to the rights, safety, or welfare of subjects.

10.1.3 Definition of Unanticipated Problems (UP)

OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of UP.

10.2   Classification of an Adverse Event

10.2.1 Severity of Event

The following guidelines will be used to describe severity.

Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

10.2.2 Relationship to Study Agent

This study will use a binary assessment:

33

- **Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
- **Not Related** – Evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

10.2.3 Expectedness

Dr. Duffy will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study medications (metformin, glibenclamide, and aspirin).

10.3 *Time period and frequency for event assessment and follow-up*

At each visit, CHWs will assess for AEs associated with medications patients are taking as part of the program. This will involve both open ended questioning ("Have you had any side effects from your medications ") and solicitation of particular serious side effects, including evidence of GI bleeding for patients taking aspirin (patients will be asked: "In the past month, have you had blood in your stool or stool that is very black and tarry ") and hypoglycemia through testing blood glucose. As noted above, GI side effects associated with metformin and hypoglycemia symptoms associated with glibenclamide without documented blood glucose ≤70 and that did require assistance from another person for treatment will not be considered AEs, as they are to be expected with regular use of these medications (~50% of patients have GI symptoms with metformin[50] and ~18% of patients taking glibenclamide[51] will have mild hypoglycemia), will be addressed through the protocol (through reduction of doses or cessation of the medication), and are transient and usually do not have lasting effects. Likewise, CHWs will screen for complications of diabetes, including angina, diabetic ulcers, and diabetic eye disease during study visits and program protocols will address the recommended management of these complications (Appendix 6). These will not be considered AEs because all patients with diabetes are at risk of these complications. Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE.

The occurrence of documented hypoglycemia (including hypoglycemia requiring emergency transport to SLMH), hypoglycemia symptoms requiring the assistance of another person for treatment, signs of GI bleeding in patients taking aspirin, and other adverse effects reported by patients that are not consistent with GI side effects of metformin or mild hypoglycemia associated with glibenclamide (miscellaneous adverse effects) will be recorded through the smartphone application used for program execution and data entry. Treatment of hypoglycemia, including emergency transport if needed, will also be executed and recorded according to the hypoglycemia protocol (Appendix 4). Patients who require transport to SLMH will be assessed and treated by Dr. Tun and his staff, who will record treatments administered and patient outcomes, including need for hospitalization and any serious sequelae of the hypoglycemic event, including death. Patients taking aspirin who are experiencing possible GI bleeding will have their aspirin discontinued and will be referred to Dr. Tun, who will record the results of any diagnostic evaluation and treatment required. Miscellaneous adverse effects of medications recorded by CHWs will be reviewed by Dr. Tun during his review of monthly patient visits (see section on "Physician supervision" in the Study Procedures section) and he will direct CHWs to take corrective action based on his clinical judgement.

Following each monthly visit, Dr. Tun will review treatment for all patients in the program. If the recommendations provided by the application and carried out by the CHWs goes against his clinical judgement, he will contact the CHW coordinators and direct them on corrective action. They will then visit the patient to follow up on their clinical status and carry out the actions recommended by Dr. Tun. When these corrective actions are necessary, Dr. Tun will communicate this to Alejandro Chavez and Dr. Duffy, who will record the reason that Dr. Tun disagreed with application recommendations and the corrective action that was recommended and carried out. Once per month, Dr. Duffy will also review all treatment data to assess for compliance to program protocols, correctness of application treatment recommendations, and occurrence of adverse events. He will communicate his findings to Dr. Svenson (PI), Alejandro Chavez, Dr. Tun, and the CHW coordinators in order to allow for corrective action and

34

ensure that the entire team is aware of all potential AEs. Dr. Duffy will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation.

10.4   Reporting procedures

10.4.1 Adverse Event Reporting
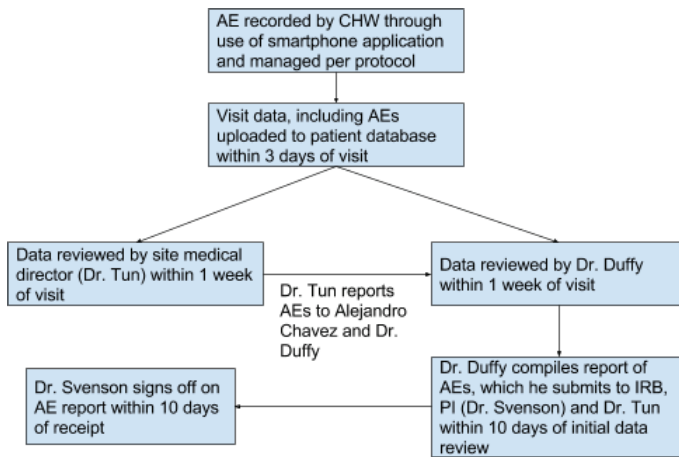
10.4.2 Serious adverse event reporting

All deaths and immediately life-threatening events, whether related or unrelated, will be recorded in an SAE report and submitted to the IRB within 24 hours of site awareness. For other SAEs, Dr. Duffy shall complete an SAE report and submit to the IRB as soon as possible, but in no event later than 10 working days after the he first learns of the effect.

```
┌─────────────────────────────┐        ┌─────────────────────────────┐
│ SAE detected by CHW during  │───────▶│ Patient managed per protocol,│
│ visit                       │        │ including emergency transport│
│                             │        │ if needed                   │
└─────────────────────────────┘        └─────────────────────────────┘
                                                      │
                                                      ▼
┌─────────────────────────────┐        ┌─────────────────────────────┐
│ Dr. Tun reports SAE to Dr.  │◀───────│ Patient evaluated by Dr. Tun │
│ Duffy within 1 day of his   │        │ within 0-3 days             │
│ evaluation                  │        │                             │
└─────────────────────────────┘        └─────────────────────────────┘
          │
          ▼
┌─────────────────────────────┐        ┌─────────────────────────────┐
│ Dr. Duffy SAE report, which │───────▶│ Dr. Svenson signs off on SAE │
│ he submits to IRB and PI    │        │ report within 7 days of      │
│ (Dr. Svenson) within 24     │        │ receipt                     │
│ hours of his awareness of   │        │                             │
│ SAE                         │        │                             │
└─────────────────────────────┘        └─────────────────────────────┘
```
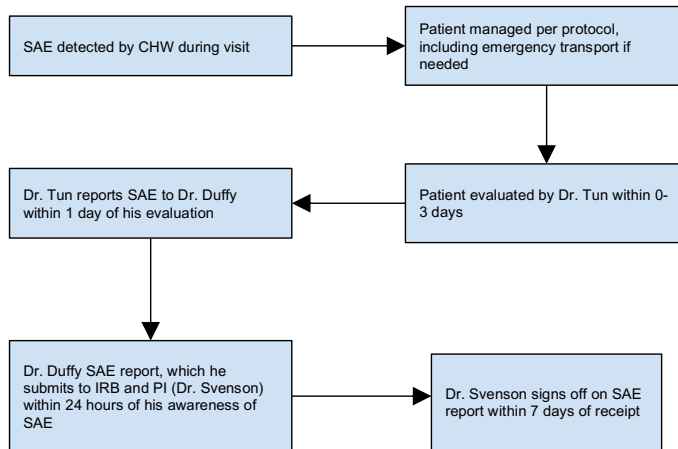
10.4.3 Unanticipated problem reporting

Dr. Duffy will be responsible for creating and completing a UP report form. Incidents that meet the OHRP criteria for UPs will be reported promptly on the following timeline:
- UPs that are SAEs will be reported to the IRB within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within 10 days of the investigator becoming aware of the problem.

The UP report will include the following information:
- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

10.4.4 Events of special interest

Events of special interest include documented hypoglycemia, probable hypoglycemia (symptoms reported by patient without hypoglycemia documented by blood glucose measurement) that required assistance from another person for treatment and incorrect recommendations given by the smartphone application.

10.4.5 Reporting of pregnancy

CHWs will ask women at risk of pregnancy (defined as premenopausal and without history of surgical sterilization) at each visit if they have reason to believe they could be pregnant. If a patient believes they could be pregnant, then a pregnancy test will be performed. If pregnancy test is positive, this patient will be referred for care through SLMH and withdrawn from the study. This will be reported to Dr. Duffy, who will subsequently report to the IRB.

Version #: 1.0

10.5   Study Halting Rules

Study suspension and revision of protocols will be considered if it appears that an inordinate number of severe adverse events are occurring. In particular, study suspension will be considered if there is an excessive incidence of severe hypoglycemia (documented BG <70 requiring emergency transfer and/or hospitalization). Estimates of the incidence of severe hypoglycemia with glibenclamide use vary, with one study reporting incidence of 7.4 episodes per 1000 person-years[52] and another reporting 57.7 episodes per 1000 person-years[53] (figure computed from study data). Given that we will enroll approximately 100 patients and follow them for 6-12 months, we will consider the occurrence of more than 3 episodes of severe hypoglycemia as warranting review of study protocols and consideration of study suspension.

10.6   Safety Oversight

Dr. Duffy will review all patient data each month to identify patient safety issues. Any issues will be promptly discussed with site investigator and medical director, Dr. Tun, and with the PI, Dr. Svenson. Special attention will be given to the following potential safety issues:
- Documented hypoglycemia. This includes those episodes requiring emergency patient transport (severe) and non-severe (those treated without complication in the field). While this is a known but side effect of glibenclamide, frequent occurrences in our patients may suggest the need for an alteration in our medication titration protocols
- Severe probable hypoglycemia (patient reports hypoglycemia symptoms that required the assistance of another person to treat due to altered mental status)
- Incorrect recommendations regarding medication dosing, management of complications, or recommendations for referral provided by the application
- AEs and UPs as described above, which would also be reported to the IRB.

Interim cumulative safety analysis will occur at 3 months, 6 months, and 9 months and final safety analysis at 12 months.

10.7   Unblinding Procedure

Not applicable

11 Study Monitoring, Auditing, and Inspecting

11.1   Medical Monitoring

11.1.1 Study Monitoring Plan

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).
- Dr. Duffy will perform both remote monitoring once per month and in-person monitoring at several points during the study. In-person monitoring will occur early in the study during the enrollment process to assist with CHW training and study logistics. He will again visit between 6 and 12 months post-enrollment for data analysis and program evaluation and improvement. Monitoring will be targeted on clinical endpoints, adverse effects, identified complications of diabetes, and accuracy of application recommendations and CHW actions
- Independent audits will not be conducted

Version #: 1.0

11.2   Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

The site PI/co-investigator/staff will be responsible for continuous vigilance to identify and report deviations to the protocol. These will be reported within 14 working days of identification of the protocol deviation, or within 14 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the IRB. Protocol deviations will be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

11.2.1 Internal Data and Safety Monitoring Board

There will be no formal DSMB. Study will be monitored as described in 11.1.1 and 10.6 and safety issues will be reported to the IRB.

11.3 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB (or their representatives) of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.).   The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

11.4 Subject Compliance Monitoring

At each visit, CHWs will assess medication compliance via patient report (see Appendix 3). Compliance with medication for diabetes is accounted for in treatment protocols and titration of medications. For patients who are noncompliant, CHWs will emphasize the importance of compliance to the patient and work with the patient to improve compliance. Patients will not be withdrawn from the study for repeated noncompliance, as this would deny them diabetes treatment and decrease the real-world applicability of our findings. Nonadherence with diabetes medications is common, with studies suggesting that only 50-75% of patients take more than 80% of their medication doses[54].

12 Ethical Considerations

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See the ARROW application for a copy of the consent form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent

form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

13 Study Finances

13.1 Funding Source

This study is funded by a seed grant from the University of Wisconsin Global Health Institute.

13.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All UW investigators will follow the UW conflict of interest policy.

14 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

15 References

Note: Includes references cited in the appendices

1. Oni T, Unwin N. Why the communicable/non-communicable disease dichotomy is problematic for public health control strategies: implications of multimorbidity for health systems in an era of health transition. *Int Health*. 2015;7(6):390-399.

2. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet*. 2006;367(9524):1747-1757.

3. World Health Organization. *Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013-2020*. WHO; 2013. http://apps.who.int/iris/bitstream/10665/94384/1/9789241506236_eng.pdf ua=1.

4. World Health Organization. *Innovative Care for Chronic Conditions - Building Blocks for Action*. WHO; 2002. http://www.who.int/chp/knowledge/publications/icccglobalreport.pdf ua=1.

5. World Health Organization. WHO | The human resources for health crisis. who.int. http://www.who.int/workforcealliance/about/hrh_crisis/en/. Published July 23, 2011. Accessed October 13, 2017.

6. World Health Organization. *Task Shifting to Tackle Health Worker Shortages*. WHO; 2007. http://www.who.int/healthsystems/task_shifting_booklet.pdf.

7. Anyangwe SCE, Mtonga C. Inequities in the global health workforce: the greatest impediment to health in sub-Saharan Africa. *Int J Environ Res Public Health*. 2007;4(2):93-100.

8. Checkley W, Ghannem H, Irazola V, et al. Management of NCD in low- and middle-income countries. *Glob Heart*. 2014;9(4):431-443.

9. Atun R, Jaffar S, Nishtar S, et al. Improving responsiveness of health systems to non-communicable diseases. *Lancet*. 2013;381(9867):690-697.

10. Samb B, Desai N, Nishtar S, et al. Prevention and management of chronic disease: a litmus test for health-systems strengthening in low-income and middle-income countries. *Lancet*. 2010;376(9754):1785-1797.

11. Tulenko K, Møgedal S, Afzal MM, et al. Community health workers for universal health-care coverage: from fragmentation to synergy. *Bull World Health Organ*. 2013;91(11):847-852.

12. Haines A, Sanders D, Lehmann U, et al. Achieving child survival goals: potential contribution of community health workers. *Lancet*. 2007;369(9579):2121-2131.

13. Christopher JB, Le May A, Lewin S, Ross DA. Thirty years after Alma-Ata: a systematic review of the impact of community health workers delivering curative interventions against malaria, pneumonia and diarrhoea on child mortality and morbidity in sub-Saharan Africa. *Hum Resour Health*. 2011;9:27.

14. Mazumder S, Taneja S, Bahl R, et al. Effect of implementation of Integrated Management of Neonatal and Childhood Illness programme on treatment seeking practices for morbidities in infants: cluster randomised trial. *BMJ*. 2014;349:g4988.

15. Vaughan K, Kok MC, Witter S, Dieleman M. Costs and cost-effectiveness of community health workers: evidence from a literature review. *Hum Resour Health*. 2015;13:71.

16. Tomlinson M, Rotheram-Borus MJ, Swartz L, Tsai AC. Scaling up mHealth: where is the evidence *PLoS Med*. 2013;10(2):e1001382.

17. Agarwal S, Perry HB, Long L-A, Labrique AB. Evidence on feasibility and effective use of mHealth strategies by frontline health workers in developing countries: systematic review. *Trop Med Int Health*. 2015;20(8):1003-1014.

18. Whitehead L, Seaton P. The Effectiveness of Self-Management Mobile Phone and Tablet Apps in Long-term Condition Management: A Systematic Review. *J Med Internet Res*. 2016;18(5):e97.

19. Arnhold M, Quade M, Kirch W. Mobile applications for diabetics: a systematic review and expert-based usability evaluation considering the special requirements of diabetes patients age 50 years or older. *J Med Internet Res*. 2014;16(4):e104.

20. Ajay VS, Prabhakaran D. The scope of cell phones in diabetes management in developing country health care settings. *J Diabetes Sci Technol*. 2011;5(3):778-783.

21. Källander K, Tibenderana JK, Akpogheneta OJ, et al. Mobile health (mHealth) approaches and lessons for increased performance and retention of community health workers in low- and middle-income countries: a review. *J Med Internet Res*. 2013;15(1):e17.

22. International Diabetes Foundation. IDF Diabetes Atlas. http://www.diabetesatlas.org/. Accessed October 13, 2017.

23. Barcelo A, Gregg EW, Gerzoff RB, et al. Prevalence of diabetes and intermediate hyperglycemia among adults from the first multinational study of noncommunicable diseases in six Central American countries: the Central America Diabetes Initiative (CAMDI). *Diabetes Care*. 2012;35(4):738-740.

24. Chary A, Greiner M, Bowers C, Rohloff P. Determining adult type 2 diabetes-related health care needs in

40

an indigenous population from rural Guatemala: a mixed-methods preliminary study. *BMC Health Serv Res*. 2012;12:476.

25. World Health Organization (WHO). *Diabetes Country Profiles, 2016 - Guatemala*. WHO; 2016. http://www.who.int/diabetes/country-profiles/gtm_en.pdf ua=1.

26. Feldman N. Stanford physicians work to protect children's health in Guatemala. Stanford News. https://news.stanford.edu/2016/06/17/stanford-physicians-use-innovation-protect-childrens-health-guatemala/. Published June 17, 2016. Accessed November 1, 2017.

27. Abegunde DO, Shengelia B, Luyten A, et al. Can non-physician health-care workers assess and manage cardiovascular risk in primary care *Bull World Health Organ*. 2007;85(6):432-440.

28. Flood D, Mux S, Martinez B, et al. Implementation and Outcomes of a Comprehensive Type 2 Diabetes Program in Rural Guatemala. *PLoS One*. 2016;11(9):e0161152.

29. Fortamet (metformin hydrochloride) dose, indications, adverse effects, interactions. Prescribers' Digital Reference. http://www.pdr.net/drug-summary/Fortamet-metformin-hydrochloride-1924.3493. Accessed November 1, 2017.

30. Glyburide (glyburide) dose, indications, adverse effects, interactions. Prescribers' Digital Reference. http://www.pdr.net/drug-summary/Glyburide-glyburide-3527. Accessed November 1, 2017.

31. Durlaza (aspirin) dose, indications, adverse effects, interactions. Prescribers' Digital Reference. http://www.pdr.net/drug-summary/Durlaza-aspirin-3789.4184. Accessed November 1, 2017.

32. American Diabetes Association. Standards of Medical Care in Diabetes - 2017. *Diabetes Care*. 2017;40(Supplement 1). http://care.diabetesjournals.org/content/diacare/suppl/2016/12/15/40.Supplement_1.DC1/DC_40_S1_final.pdf.

33. International Diabetes Federation Guideline Development Group. Global guideline for type 2 diabetes. *Diabetes Res Clin Pract*. 2014;104(1):1-52.

34. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2017 Executive Summary. *Endocr Pract*. 2017;23(2):207-238.

35. McCulloch DK. Metformin in the treatment of adults with type 2 diabetes. UpToDate. https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus. Published April 4, 2017.

36. Bailey CJ, Turner RC. Metformin. *N Engl J Med*. 1996;334(9):574-579.

37. Rambiritch V, Maharaj B, Naidoo P. Glibenclamide in patients with poorly controlled type 2 diabetes: a 12-week, prospective, single-center, open-label, dose-escalation study. *Clin Pharmacol*. 2014;6:63-69.

38. Schopman JE, Simon ACR, Hoefnagel SJM, Hoekstra JBL, Scholten RJPM, Holleman F. The incidence of mild and severe hypoglycaemia in patients with type 2 diabetes mellitus treated with sulfonylureas: a systematic review and meta-analysis. *Diabetes Metab Res Rev*. 2014;30(1):11-22.

39. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease. *Circulation*.

Field Code Changed
Field Code Changed
Field Code Changed
Field Code Changed
Field Code Changed
Field Code Changed

2012;126(25):e354-e471.

40. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(7):2160-2236.

41. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes. *Circulation*. 2014;130(25):e344-e426.

42. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. *Circulation*. January 2012:CIR.0b013e3182742cf6.

43. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2010;(4):CD002967.

44. Volman B, Laing R, Reed T, Ewen MM. *Direct Costs and Availability of Diabetes Medicines in Low-Income and Middle-Income Countries*. World Health Organization; 2008. http://apps.who.int/medicinedocs/documents/s18387en/s18387en.pdf.

45. Agency for Healthcare Research and Quality. Use the Teach-Back Method: Tool #5 | Agency for Healthcare Research & Quality. www.ahrq.gov. https://www.ahrq.gov/professionals/quality-patient-safety/quality-resources/tools/literacy-toolkit/healthlittoolkit2-tool5.html. Published January 30, 2015. Accessed October 19, 2017.

46. A1CNow+ System. PTS Diagnostics. http://www.ptsdiagnostics.com/a1cnow-plus.html. Accessed October 20, 2017.

47. World Health Organization. *WHO PEN Protocol 1: Prevention of Heart Attacks, Strokes and Kidney Disease through Integrated Management of Diabetes and Hypertension*. World Health Organization; 2013. http://www.who.int/ncds/management/Protocol1_HeartAttack_strokes_kidneyDisease.pdf.

48. Kohn M. Effect size for before-after study (Paired T-test) - Sample Size Calculators. UCSF Clinical and Translational Science Institute - Sample Size Calculators. http://www.sample-size.net/effect-size-study-paired-t-test/. Published January 25, 2016. Accessed October 28, 2017.

49. Chang A, Frank J, Knaebel J, Fullam J, Pardo S, Simmons DA. Evaluation of an over-the-counter glycated hemoglobin (A1C) test kit. *J Diabetes Sci Technol*. 2010;4(6):1495-1503.

50. Lexicomp. Metformin: Drug Information. UpToDate. https://www.uptodate.com/contents/metformin-drug-information source=see_link.

51. Gangji AS, Cukierman T, Gerstein HC, Goldsmith CH, Clase CM. A systematic review and meta-analysis of hypoglycemia and cardiovascular events: a comparison of glyburide with other secretagogues and with insulin. *Diabetes Care*. 2007;30(2):389-394.

52. Douros A, Yin H, Yu OHY, Filion KB, Azoulay L, Suissa S. Pharmacologic Differences of Sulfonylureas and the Risk of Adverse Cardiovascular and Hypoglycemic Events. *Diabetes Care*. 2017;40(11):1506-1513.

53. Clemens KK, McArthur E, Dixon SN, Fleet JL, Hramiak I, Garg AX. The Hypoglycemic Risk of Glyburide (Glibenclamide) Compared with Modified-Release Gliclazide. *Can J Diabetes*. 2015;39(4):308-316.

54. Capoccia K, Odegard PS, Letassy N. Medication Adherence With Diabetes Medication: A Systematic Review of the Literature. *Diabetes Educ*. 2016;42(1):34-71.

55. Mora S, Manson J, Ames J. *Practical Algorithm for Shared Decision Making in the Use of Low-Dose Aspirin in Primary Prevention of ASCVD*. Harvard University; 2016. https://s3.amazonaws.com/aspiringuideresources/AspirinAlgorithm.pdf.

56. Bujanda L, Gutiérrez-Stampa MA, Caballeros CH, Alkiza ME. [Gastrointestinal disorders in Guatemala and their relationship with parasitic infections]. *An Med Interna*. 2002;19(1):3-6.

57. Gehi AK, Ali S, Na B, Whooley MA. Self-reported medication adherence and cardiovascular events in patients with stable coronary heart disease: the heart and soul study. *Arch Intern Med*. 2007;167(16):1798-1803.

58. Garfield S, Clifford S, Eliasson L, Barber N, Willson A. Suitability of measures of self-reported medication adherence for routine clinical use: a systematic review. *BMC Med Res Methodol*. 2011;11:149.

59. Sola D, Rossi L, Schianca GPC, et al. Sulfonylureas and their use in clinical practice. *Arch Med Sci*. 2015;11(4):840-848.

60. Cox DJ, Gonder-Frederick L, Antoun B, Cryer PE, Clarke WL. Perceived symptoms in the recognition of hypoglycemia. *Diabetes Care*. 1993;16(2):519-527.

61. Cryer P. Management of hypoglycemia during treatment of diabetes mellitus. UpToDate. https://www.uptodate.com/contents/management-of-hypoglycemia-during-treatment-of-diabetes-mellitus source=search_result&search=hypoglycemia%20diabetes&selectedTitle=1~150. Published November 8, 2016.

62. Low Blood Glucose (Hypoglycemia) | NIDDK. National Institute of Diabetes and Digestive and Kidney Diseases. https://www.niddk.nih.gov/health-information/diabetes/overview/preventing-problems/low-blood-glucose-hypoglycemia. Accessed October 11, 2017.

63. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care*. 2013;36(5):1384-1395.

64. Graz B, Dicko M, Willcox ML, et al. Sublingual sugar for hypoglycaemia in children with severe malaria: a pilot clinical study. *Malar J*. 2008;7:242.

65. Barennes H, Valea I, Nagot N, Van de Perre P, Pussard E. Sublingual sugar administration as an alternative to intravenous dextrose administration to correct hypoglycemia among children in the tropics. *Pediatrics*. 2005;116(5):e648-e653.

66. Bösner S, Haasenritter J, Becker A, et al. Ruling out coronary artery disease in primary care: development and validation of a simple prediction rule. *CMAJ*. 2010;182(12):1295-1300.

67. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*. 1992;101(6):1644-1655.

68. Lexicomp. Glyburide: Drug Information. UpToDate. https://www.uptodate.com/contents/glyburide-glibenclamide-drug-information source=search_result&search=glyburide&selectedTitle=1~55.

69. Funnell M. Low Blood Glucose (Hypoglycemia) | NIDDK. National Institute of Diabetes and Digestive and Kidney Diseases. https://www.niddk.nih.gov/health-information/diabetes/overview/preventing-problems/low-blood-glucose-hypoglycemia. Published August 2016. Accessed November 3, 2017.

Appendices

Appendix 1 - Screening Questions, Demographic Information, and Past Medical History

Screening Questions for Program Participation
- "Have you been diagnosed with diabetes "[1] (Y/N)
  - If NO, application comes to a hard stop and the patient is advised that this program is only for patients who have been diagnosed with diabetes
  - If YES, "Have you been told that your diabetes is type 1 diabetes " (Y/N)
    - If YES, application comest to a hard stop and the patient is advised that the program is only for patients with type 2 diabetes. Patient is referred to San Lucas Mission Hospital for further cares
    - If NO, application proceeds to the next question
- "Are you 18 years of age or older " (Y/N)
  - If YES, application continues to the next question
  - If NO, application comes to a hard stop and the patient is advised that the program is not for patients younger than age 18. Patient is referred to San Lucas Mission Hospital for further cares
- "Are you taking insulin for your diabetes " (Y/N)
  - If NO, application continues to the next question
  - If YES, application comes to a hard stop and the patient is advised that the program is not for patients who require insulin to control their diabetes. Patient is referred to San Lucas Mission Hospital for further cares.
- Application prompts promoter[2], "What is the patient's sex " (M/F)
  - If M, application proceeds to next section
  - If F, application prompts promoter to ask patient "Are you currently pregnant " (Y/N/UNSURE)
    - "Have you gone through menopause " (Y/N)
      - If YES, application continues to enrollment procedures
      - If NO, application continues to next question
    - "Have you had a tubal ligation " (Y/N)
      - If YES, application continues to enrollment procedures
      - If NO, application continues to next question
    - "Are you currently pregnant " (Y/N/UNSURE)[3]
      - If NO, application proceeds to next section
      - If YES, application comes to a hard stop and the patient is advised that the program is not designed for pregnant women with diabetes. Patient is referred to San Lucas Mission Hospital for further cares.
      - If UNSURE, urine pregnancy test is conducted
        - If NEGATIVE, application proceeds to next section
        - If POSITIVE, application comes to a hard stop and the patient is advised that the program is not designed for pregnant women with diabetes. Patient is referred to San Lucas Mission Hospital for further cares.

---

[1] Unless otherwise specified, questions or other elements in quotation marks are addressed to the patient
[2] Promoter=Community Health Worker (CHW)
[3] Female patients will be assessed for possible pregnancy in this way at monthly visits as well

44

Version #: 1.0

Basic Demographic Information
- Application prompts promoter to enter name, sex, and community (from pull down menu prepopulated with all possible communities)
- Application asks the promoter: "Is the exact date of birth known " (Y/N)
    - If YES, application prompts promoter to enter DOB and calculates age from this
    - If NO, application prompts patient to enter age in years
- Application asks promoter: "What language does the patient prefer to communicate in ". Possible responses are Spanish or Kaqchikel and are selected from a drop down menu

Past Medical History
- "How many years have you had diabetes " (accepts integers 0-100)
- "Where were you diagnosed " (Pull down menu with common sites/means of diabetes diagnosis: San Lucas Hospital, government health center, IGSS[4], health promoter, visit from foreign doctor, private doctor or nurse, other)
- Application asks promoter: "Does the patient have IGSS " (Y/N)
- "Do you smoke " (Y/N)
- "Do you take natural medicines for diabetes "[5] (Y/N)
- "Have you had any of the following conditions or illnesses " (application allows for selection of any of the below options)[6]:
    - Cancer
    - Emphysema/COPD
    - Chronic kidney disease
    - Heart attack
    - Stroke
    - High blood pressure (hypertension)
    - None of these (can't be selected if other option is selected)
- If option selected for "stroke", application prompts promoter to ask: "Was the stroke caused by bleeding in the brain " (Y/N)

Appendix 2 - Aspirin for Secondary Prevention of ASCVD

Eligibility for aspirin for secondary prevention (information collected from Past Medical History section of enrollment protocol)
- Patient with prior history of myocardial infarction
- Patients with prior history of non-hemorrhagic stroke

Current aspirin use → "Are you currently taking aspirin every day "

---

[4] Instituto Guatemalteco de Seguro Social - Guatemalan social security program which provides health services and runs hospital and clinics for members of the public who work in eligible jobs
[5] A community needs assessment conducted to support this project found that some patients would use traditional medications to treat diabetes, particularly when prescription medications were not available. Thus, we ask this question to monitor how common the use of traditional medications is in the population
[6] Patients with 2 or more chronic conditions (excluding hypertension) will have a relaxed glycemic goal

Version #: 1.0

- If YES, application prompts promoter to enter milligram amount of daily aspirin dose in a numeric entry box
- If NO, application skips to the next section

Determining if contraindications or need for precautions are present[7]
- "Have you ever had an allergy to aspirin causing difficulty breathing, low blood pressure, or other severe illness " (Y/N)
  - If YES, aspirin not prescribed
  - If NO, continue to next question
- "Have you recently had blood in your stool or black and tarry stools " (Y/N)
  - If YES, aspirin not prescribed, referred to medical director for further recently
  - If NO, continue to next question
- "Have you ever had a stomach ulcer " (Y/N)
  - If YES, aspirin prescribed and patient recommended to take omeprazole or ranitidine while taking aspirin
  - If NO, continue to next question
- "Do you have frequent pain in the upper part of your belly or heartburn " (Y/N)
  - If YES, aspirin prescribed and patient recommended to take omeprazole or ranitidine while taking aspirin
  - If NO, aspirin prescribed
- Blood pressure measured later in the visit
  - If BP<160/100 mmHg, aspirin prescribed
  - BP ≥160/100 mmHg → referred to medical director for BP management, aspirin not prescribed until BP better-controlled

Appendix 3 - Medication History, Side Effects, and Adherence

Medication History
- "Are you taking Metformin " (Y/N)
  - If NO, application skips to next question
  - If YES, "Are you only taking 1 pill size of Metformin " (Y/N)
    - If YES, "How many milligrams are the Metformin pills " (can select 500 mg, 850 mg, or 1000 mg, which are commonly available sizes in the area) and "How many Metformin pills do you take daily " (select from ½, 1, 2, 3, and 4)
    - If NO, "How many milligrams of Metformin do you take in total per day " (numeric entry box)
- "Are you taking Glibenclamide " (Y/N)
  - If NO, application skips to next question
  - If YES, "Are you only taking 1 pill size of Glibenclamide " (Y/N)
    - If YES, "How many milligrams are the Glibenclamide pills " (select 5 mg or 10 mg, the commonly available sizes in the area) and "How many Glibenclamide pills do you take daily " (select ½, 1, 2, 3, or 4)

---

[7] These considerations are based on the Aspirin Guide clinical decision support tool[55], which provides guidance on the use of ASA in primary and secondary ASCVD prevention and is in turn based on guidance from the USPSTF

46

- ■ If NO, "How many milligrams of Glibenclamide do you take in total per day " (numeric entry box)
- "Are you taking any other medication for diabetes prescribed by a doctor " (Y/N)
  - If NO, application skips to next question
  - If YES, application prompts promoter to enter medication name (free text), milligram strength of pills (numeric entry), and number of pills per day (½, 1, 2, 3, or 4)
- If patient not currently taking any medication, application prompts promoter to ask, "Have you previously taken medication for diabetes " (Y/N)
  - If YES, questions regarding medication side effects appear (These also appear if patient is taking any of the aforementioned medications)
  - If NO, application skips to the next section
- "Are you currently taking medication for high blood pressure " (Y/N)
  - If YES
    - ■ Application prompts promoter to collect information about name of medication (free text) and dosage (numeric entry)
    - ■ Renal function testing will be recommended for this patient
    - ■ Application skips to the next section
  - If NO, application skips to the next section

Assessing for Medication Side Effects
- "Have you had any side effects from your medications " (Y/N)
  - If NO, application skips to the next section
  - If YES, application prompts promoter to ask the patient: "What problems have you had with your medication "[8]
  - Application asks promoter: "Has the patient complained of nausea, vomiting, or persistent diarrhea after taking Metformin " (Y/N)
    - ■ If YES, application prompts promoter to ask patient: "Have you skipped a dose of metformin, or thought about stopping metformin due to these symptoms "
      - If YES, patient is considered to be having significant metformin side effects
      - If NO, patient is not considered to be having significant metformin side effects
    - ■ If NO, application prompts promoter to enter other symptoms in a free text box for review by the physician
  - For patients taking aspirin (for monthly visit only): "In the past month, have you had blood in your stool or stool that is very black and tarry "
    - ■ If YES, patient is advised to stop aspirin and is referred to medical director for further assessment
    - ■ If NO, aspirin is continued

Assessing Medication Adherence
- "In the past month, how often did you take your medication as the doctor prescribed "[9]

---

[8] This question about medication side effects is asked in an open-ended fashion rather than a specific fashion (e.g. "have you experienced nausea, vomiting or diarrhea after taking metformin") so as to not bias towards positive answers, given the high prevalence of gastrointestinal symptoms in Guatemalan patients, thought to be due in part to frequent exposure to and infection with gastrointestinal parasites[56]

[9] This question has been shown to predict outcomes in patients with chronic heart disease, as a proxy for medication adherence[57]. It was also chosen for its simplicity. While self-reporting measures for adherence have been shown to correlate with objective adherence data, over-reporting of adherence is common[58]. For this reason

Version #: 1.0

- ○ Answer choices (select one): All of the time (100%), Nearly all of the time (90%), Most of the time (75%), About half the time (50%), Less than half the time (<50%)
- ○ Scoring
  - ■ Those responding "All of the time" or "Nearly all of the time" are considered to be adherent
  - ■ Those responding "Most of the time" or less are considered to be non-adherent
- ● "Did you take your full dosage of glibenclamide yesterday "[10] (Y/N)
  - ○ If YES, application skips to the next question
  - ○ If NO, application prompts promoter to ask patient "Did you take your full dosage of glibenclamide today " (Y/N) → application moves on to the next section with either answer

Appendix 4 - Hypoglycemia Protocol

Protocol for identifying probable hypoglycemic episodes
- ● Patients who are taking glibenclamide are asked the following questions:
  - ○ "In the last month, have you had episodes of any of the following symptoms"[11]:
    - ■ Confusion
    - ■ Trembling
    - ■ Feeling uncoordinated
    - ■ Palpitations
    - ■ Abnormal sweating
    - ■ Abnormal anxiousness
  - ○ Patients reporting episodes of any of these symptoms are asked the following questions and their answers are scored as noted:
    - ■ "Did these symptoms come on gradually or did they start suddenly[12] "
      - ● Gradually (0)
      - ● Suddenly (+1)
    - ■ "Did these symptoms occur when you had not eaten for several hours or after strenuous physical activity[13] "
      - ● Yes (+1)
      - ● No (0)
    - ■ "Did these symptoms improve after eating something "
      - ● Yes (+1)
      - ● No (0)
- ● Patient considered to have probable hypoglycemia if above answers total to 2 or more points

---

[10] Glibenclamide functions as an insulin secretagogue and has a duration of action of ~24 hours[59]. Thus, it is expected to have a relatively short-term effect on blood glucose and it is essential to know the timing of the last dose when interpreting and acting on a patient's blood glucose level.

and because the original validation study used this standard as well, we define adherence as taking medication "Nearly all of the time" or "All of the time".

[11]These symptoms were found to be the most highly correlated with experimentally-induced hypoglycemia[60,61].

[12] In general, the onset of hypoglycemia symptoms is rapid rather than gradual[62]

[13] This question assesses for the association of symptoms with two common risk factors for hypoglycemia that are likely to be present in our population[63]

Version #: 1.0

- Patients who have 2 or more points are asked the following question: "When you had these symptoms, were you so confused or sleepy that someone else needed to help you eat or drink something with sugar ˮ
    - If YES, this is considered as an episode of probable severe hypoglycemia
    - If NO, this is considered an episode of probable mild hypoglycemia

Protocol for management of hypoglycemia detected with blood glucose testing during patient visit
- 1st glucose reading is <70
    - Follow Up Question: "Is the patient unresponsive, very sleepy or confused ˮ
        - YES: Unresponsive, very sleepy, or confused
            - Message: "Call a coordinator. The patient should be transported to the hospital immediately. The patient needs something with sugar (candy, juice, coke) immediately. If the patient is unable to drink something, sprinkle sugar under the tongue[14]."
        - NO: Normal mental status
            - Message: "Blood sugar is low. Please re-test to confirm."
            - Re-test to confirm
- Promoter repeats blood glucose (reading 2)
    - Reading 2 ≥70
        - Message: "It is now in normal range. Continue with the questions."
    - Reading 2 <70
        - Message: "It remains very low. The patient should eat something with sugar (candy, juice, coke) immediately". The app also provides a list of options for 15 grams of simple carbohydrate.
        - Message: "Wait 15 minutes after eating and re-test."
        - Re-test after eating and waiting 15 minutes
    - Reading 2 ≥400
        - Message: "Drastic change. Please start over."
- Promoter repeats blood glucose (reading 3)
    - Reading 3 ≥70
        - Message: "It is now in a normal range. The patient should eat a full meal to prevent the blood sugar from dropping again. Continue with the questions after the patient has eaten."
        - Recommendation: "Be vigilant and seek medical attention if you begin to feel bad. You should have someone with you for the rest of the day"
        - Application will lower dosage of glibenclamide
    - Reading 3 <70
        - Message: "It remains very low. The patient should eat something with sugar (candy, juice, coke) immediately". The app also provides a list of options for 15 grams of simple carbohydrate.
        - Message: "Wait 15 minutes after eating and re-test."
        - Re-test after eating and waiting 15 minutes
- Promoter repeats blood glucose if indicated (reading 4)
    - Reading 3 ≥70

---

[14] Table sugar sprinkled under the tongue has been shown to be comparable to intravenous glucose for the treatment of severe hypoglycemia in two small studies performed in resource-limited settings[64,65]

Version #: 1.0

- ■ Message: "It is now in a normal range. The patient should eat a full meal to prevent the blood sugar from dropping again. Continue with the questions after the patient has eaten."
- ■ Recommendation: "Be vigilant and seek medical attention if you begin to feel bad. You should have someone with you for the rest of the day. Do not take your glibenclamide today"
- ■ Application will lower dosage of glibenclamide
  - ○ Reading 3 <70
    - ■ Message: "It remains very low. The patient should eat something with sugar (candy, juice, coke) immediately if they are still alert and able to eat and drink. If they are not responding or very sleepy, sprinkle sugar under the tongue. Call the coordinator to arrange transport to the hospital for further treatment and monitoring"

Appendix 5 - Hyperglycemia Protocols

Hyperglycemia
- ● 400≤FBG<HI
  - ○ Urgent MD visit recommended in all cases
    - ■ Patient willing to go
      - ● Dispense 5 days' worth of meds as a bridge based on 180(200)≤FBG<400 recommendations (if monthly visit) or A1c (month 3 or enrollment)
      - ● Arrange appointment
    - ■ Patient unwilling to go
      - ● Dispense medications based on 180(200)≤FBG<400 recommendations (if monthly visit) or A1c (month 3 or enrollment)
      - ● Follow up in 1-3 days
- ● FBG=HI
  - ○ Emergent visit recommended in all cases
    - ■ Patient willing to go → arrange emergency transport
    - ■ Patient not willing to go
      - ● Dispense medications based on 180(200)≤FBG<400 recommendations (if monthly visit) or A1c (month 3 or enrollment)
      - ● Follow up in 1 day
- ● PPBG=HI
  - ○ "Is the patient unresponsive, very sleepy, or confused" (Y/N)
    - ■ If YES, emergency visit recommended
      - ● Patient willing to go → arrange emergency transport
      - ● Patient not willing to go
        - ○ Dispense medications based on 180(200)≤FBG<400 (if monthly visit) or A1c (month 3 or enrollment) recommendations
        - ○ Follow up later that day or the next day
    - ■ If NO
      - ● CHW advises patient to increase water intake
      - ● Dispense medications based on 180(200)≤FBG<400 recommendations (if monthly visit) or A1c (month 3 or enrollment)
      - ● Follow up with FBG in 1-3 days

Version #: 1.0

Appendix 6 - Complications of Diabetes Protocols

Chest Pain[15]
- "In the past month, have you had chest pain ﾠ"
  - If NO, application skips to the next topic in the visit
  - If YES, application initiates triage protocols as below
- Application uses demographic data already entered to score the following risk factors:
  - Male ≥55 years (+1)
  - Female ≥65 years (+1)
  - History of heart attack or stroke (+1)
- Application prompts promoter to ask the following YES/NO questions:
  - "Do you have chest pain right now ﾠ" (used for determining timing of referral)
  - "Does the pain worsen or start with strenuous physical activity" (+1 if YES)
  - "Can you bring about the pain by pressing on the chest" (+1 if NO)
  - "Do you think the pain is coming from your heart" (+1 if YES)
- Application uses these responses to make recommendations:
  - 3-5 points, current pain → Give aspirin (four 81 mg tablets), call ambulance
  - 3-5 points, no current pain →Aspirin 81 mg daily, urgent visit
  - 2 points, current pain → Aspirin 81 mg daily, urgent visit
  - 2 points, no current pain → Aspirin 81 mg daily, non-urgent visit
  - 0 or 1 points, with or without current pain → Very low risk of CAD. No treatment or follow up needed at this time
- Prior to aspirin administration, application prompts CHW to ask: "Have you ever had an allergy to aspirin causing difficulty breathing, low blood pressure, or other severe illness ﾠ" (Y/N)
  - If YES, aspirin administered
  - If NO, not administered
- If ambulance transfer recommended, but patient refuses, application advices aspirin dosing as above promoter follow up the next day

Diabetic Ulcers
- Promoter asks patient: "Do you have wounds that won't heal on your legs or feet ﾠ"
  - If NO, application skips to the next topic in the visit
  - If YES, application initiates triage protocols as below
- Application prompts promoter to examine the patient's feet to assess for the following signs of infection:
  - Redness, warmth, swelling, and/or soreness of the skin around the ulcer
  - Copious or purulent secretions, foul odor
- If NO signs of infection, application recommends referral to doctor for routine visit sometime in the next 1-2 weeks
- If there are signs of infection, the following triage protocols are initiated:

---

[15] The ability to treat CAD and ACS in the San Lucas area is very limited. Chest pain is also a common symptom in primary care settings and is usually non-cardiac in origin. Thus, we tried to design an approach to possible symptoms of CAD/ACS in our relatively high-risk population that would detect patients with concerning presentations while at the same time limiting false positives, which could place a significant burden on the local health system. We have adopted a clinical prediction rule for identifying patients with chest pain who are at high risk of CAD. This rule relies on history alone and was validated in a primary care population[66]

Version #: 1.0

- ○ Promoter prompted to check patient's oral temperature with digital thermometer
- ○ Application reviews previously collected blood pressure and pulse (both obtained with automatic blood pressure cuff)
- ○ If temperature >100.4 F (38 C) OR <96.8 F (36 C) OR pulse >90, OR systolic BP <90 mmHg → patient screens positive for possible systemic infection and/or sepsis, application prompts promoter to arrange immediate transport to the hospital[16]
- ○ If vitals do not screen positive for possible sepsis, the patient is referred to the doctor for an urgent appointment (within the next 1-2 days)

Ophthalmic Complications
- ● Promoter asks patient: "In the past month, have you had problems with your vision "
  - ○ If NO, application skips to the next topic in the visit
  - ○ If YES, application initiates triage questions as below
- ● Promoter asks patient: "Do these problems with your vision come and go, or are they constant "
  - ○ If INTERMITTENT, application prompts promoter to advise patient that this is likely due to periods of high blood sugar and these vision problems should improve with better control of diabetes. Application then skips to next topic in the visit
  - ○ If CONSTANT, application continues triage questions as below
- ● Promoter asks patient "Has your vision worsened in the past month "
  - ○ If YES, application recommends urgent referral to doctor
  - ○ If NO, applications recommend that patients see doctor if having worsening vision problems

Appendix 7 - Referrals Protocols

Referrals processes
- ● Routine referrals
  - ○ Timeframe: within 1-2 weeks
  - ○ CHW recommends that patient seek care and explains why this referral is necessary
  - ○ Patient travels to San Lucas to seek a consult with medical director Dr. Rafael Tun at San Lucas Mission Hospital (SLMH)
- ● Urgent referrals
  - ○ Timeframe: within 1-2 days
  - ○ CHW recommends referral to patient, explains rationale and emphasizes that this should occur as soon as possible
  - ○ Patient provided with written referral
  - ○ CHW informs CHW coordinator of urgent referral
  - ○ Patient travels to San Lucas to seek a consult with medical director Dr. Rafael Tun at San Lucas Mission Hospital (SLMH). Written referral note allows them to skip the queue to be seen by Dr. Tun
- ● Emergency referrals

---

[16] All three of these vitals criteria are taken from the SIRS/sepsis criteria initially defined in 1992[67]. While the qSOFA score is now recommended for sepsis screening, these older criteria were chosen because they are all objective and can be collected by automated devices (digital thermometer and automatic blood pressure cuff), limiting user error by community health workers. In addition, if any of the three criteria are present, we consider this a positive screen and the application recommends transfer for immediate care. We expect that this will increase sensitivity for detection of systemic infection and/or sepsis

52

Version #: 1.0

- ○ Time frame: same day, as soon as possible
- ○ CHW recommends emergency transport to patient
- ○ CHW calls SLMH to arrange for ambulance transport of the patient

Indications for referrals
- Routine referrals
  - ○ Stage I hypertension (BP 140-160/90-100 mmHg)
  - ○ Non-infected diabetic ulcer
  - ○ Need for renal function testing
  - ○ A1c ≥9 despite maximal doses of metformin and glibenclamide for ≥3 months
  - ○ A1c ≥9 for 3 consecutive checks
  - ○ A1c above glycemic target, but less than 9 for 4 consecutive checks
  - ○ Recent chest pain, moderate risk (2 of 5 points[17])
  - ○ Blood in stool or possible melena
  - ○ Patient has other symptoms not addressed by the program protocols
- Urgent referrals
  - ○ Stage II hypertension (BP 160-200/100-120 mmHg)
  - ○ Possibly infected diabetic ulcer, no signs of systemic infection
  - ○ Worsening vision
  - ○ FBG detectable, but ≥400
  - ○ A1c ≥14
  - ○ Patient cannot tolerate minimum doses of metformin and/or glibenclamide
  - ○ Current chest pain, moderate risk (2 of 5 points)
- Emergency referrals
  - ○ Severe hypertension (BP ≥200/120 mmHg)
  - ○ Fasting blood glucose undetectable high
  - ○ Postprandial/random blood glucose undetectable high with mental status changes
  - ○ Hypoglycemia associated with altered mental status
  - ○ Persistent hypoglycemia despite treatment in the field
  - ○ Current chest pain, high risk (≥3 of 5 points)
  - ○ Possibly infected diabetic ulcer with signs of systemic infection

Appendix 8 - Enrollment Medication Dosing Recommendations

A1c <5.7
1. Not taking medications→ Does not have diabetes. Retest in A1c in 1 year
2. Nonadherent with medications → May not have diabetes or may have diet-controlled diabetes. Stop medications and retest A1c in 3 months
3. Taking metformin without problems
   a. Metformin 500-1000 mg → metformin 850 mg
   b. Metformin 1500-2550 mg → metformin 1700 mg
4. Taking metformin with problems
   a. Metformin 500-850 mg, refuses to take metformin → Stop medications, retest in 3 months
   b. Metformin 500-850 mg, agrees to take metformin → metformin 850 mg
   c. Metformin 1000-1700 mg → metformin 850 mg

---

[17] See Appendix 6 for further details of risk assessment in patients with chest pain

Version #: 1.0

d. Metformin 2000-2550 mg → metformin 1700 mg
5. Taking glibenclamide, with or without hypoglycemia or hypoglycemia symptoms
    a. All doses → metformin 1700 mg
6. Taking glibenclamide, previous problems with metformin
    a. All doses, agree to take metformin → metformin 850 mg
    b. All doses, refuses to take metformin → discontinue medications, recheck A1c in 3 months
7. Taking glibenclamide with hypoglycemia or hypoglycemia symptoms, previous problems with metformin
    a. All doses, agrees to take metformin → metformin 850 mg
    b. All doses, refuses to take metformin → stop medications, recheck A1c in 3 months
8. Taking metformin and glibenclamide, with or without hypoglycemia or hypoglycemia symptoms
    a. Metformin 500-1000 mg + glibenclamide any dose → metformin 850 mg
    b. Metformin 1500-2550 mg + glibenclamide any dose → metformin 1700 mg
9. Taking metformin and glibenclamide, problems with metformin
    a. Metformin 500-850 mg + glibenclamide any dose, agrees to take metformin → metformin 850 mg
    b. Metformin 500-850 mg + glibenclamide any dose, refuses to take metformin → stop medications, recheck A1c in 3 months
    c. Metformin 1000-1700 mg + glibenclamide any dose → metformin 850 mg
    d. Metformin 2000-2550 mg + glibenclamide any dose → metformin 1700 mg
10. Taking metformin and glibenclamide, with hypoglycemia or hypoglycemia symptoms, problems with metformin
    a. Metformin 500-850 mg + glibenclamide any dose, agrees to take metformin → metformin 850 mg
    b. Metformin 500-850 mg + glibenclamide any dose, refuses to take metformin → stop medications, recheck A1c in 3 months
    c. Metformin 1000-1700 mg + glibenclamide any dose → metformin 850 mg
    d. Metformin 2000-2550 mg + glibenclamide any dose → metformin 1700 mg

5.7≤ A1c <6.5
1. Not taking medications → Patient has prediabetes. Counsel on diet and exercise and retest yearly
2. Nonadherent with medications → May have diabetes. Stop medications and recheck A1c in 3 months
3. Taking metformin without problems
    a. Metformin 500-1000 mg → metformin 850 mg
    b. Metformin 1500-2550 mg → metformin 1700 mg
4. Taking metformin with problems
    a. Metformin 500-850 mg, refuses to take metformin → Stop medications, retest A1c in 3 months
    b. Metformin 500-850 mg, agrees to take metformin → metformin 850 mg
    c. Metformin 1000-1700 mg → metformin 850 mg
    d. Metformin 2000-2550 mg → metformin 1700 mg
5. Taking glibenclamide, with or without hypoglycemia or hypoglycemia symptoms
    a. All doses → metformin 1700 mg
6. Taking glibenclamide, previous problems with metformin, with or without hypoglycemia or hypoglycemia symptoms
    a. All doses, agrees to take metformin → metformin 850 mg
    b. All doses, refuses to take metformin → stop medications, recheck A1c in 3 months
7. Taking metformin and glibenclamide, with or without hypoglycemia or hypoglycemia symptoms
    a. Metformin 500-1000 mg + glibenclamide any dose → metformin 850 mg
    b. Metformin 1500-2550 mg + glibenclamide any dose → metformin 1700 mg

8. Taking metformin and glibenclamide, problems with metformin, without hypoglycemia or hypoglycemia symptoms
    a. Metformin 500-850 mg + glibenclamide any dose, agrees to take metformin → metformin 850 mg
    b. Metformin 500-850 mg + glibenclamide any dose, refuses to take metformin → glibenclamide 2.5 mg
    c. Metformin 1000-1700 mg + glibenclamide any dose → metformin 850 mg
    d. Metformin 2000-2550 mg + glibenclamide any dose → metformin 1700 mg
9. Taking metformin and glibenclamide, with hypoglycemia or hypoglycemia symptoms, problems with metformin
    a. Metformin 500-850 mg + glibenclamide any dose, agrees to take metformin → metformin 850 mg
    b. Metformin 500-850 mg + glibenclamide any dose, refuses to take metformin → stop medications, recheck A1c in 3 months
    c. Metformin 1000-1700 mg + glibenclamide any dose → metformin 850 mg
    d. Metformin 2000-2550 mg + glibenclamide any dose → metformin 1700 mg

6.5≤ A1c ≤Tx goal
1. Not taking medications or nonadherent, no hypoglycemia or hypoglycemia symptoms, no problems with metformin → metformin 1700 mg
2. Not taking medications or nonadherent, no hypoglycemia or hypoglycemia problems, problems with metformin
    a. Agrees to take metformin → metformin 850 mg
    b. Refuses to take metformin → glibenclamide 2.5
3. Not taking medications or nonadherent, hypoglycemia or hypoglycemia symptoms, problems with metformin
    a. Agrees to take metformin → metformin 850 mg
    b. Refuses to take metformin, prescribed glibenclamide >2.5 mg → glibenclamide 2.5 mg
    e. Refuses to take metformin, prescribed glibenclamide 2.5 mg → MD consult
4. Taking metformin without problems
    a. Metformin 500-1000 mg → metformin 850 mg
    b. Metformin 1500-2550 mg → metformin 1700 mg
5. Taking metformin with problems
    a. Metformin 500-850 mg, agrees to take metformin → metformin 850 mg
    b. Metformin 500-850 mg, refuses to take metformin → glibenclamide 2.5 mg
    c. Metformin 1000-1700 mg → metformin 850 mg
    d. Metformin 2000-2550 mg → metformin 1700 mg
6. Taking glibenclamide without problems
    a. All doses → metformin 1700 mg
7. Taking glibenclamide without problems, previous problems with metformin
    a. Willing to take metformin
        i. Glibenclamide 2.5 mg → metformin 850 mg
        ii. Glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
        iii. Glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
        iv. Glibenclamide 15-20 mg → metformin 850 mg + glibenclamide 10 mg
    b. Refuses to take metformin
        i. Glibenclamide 2.5-10 mg → continue current dose of glibenclamide
        ii. Glibenclamide 15-20 mg → glibenclamide 10 mg
8. Taking glibenclamide with hypoglycemia or hypoglycemia symptoms

55

      a.   All doses → metformin 1700 mg
9. Taking glibenclamide with hypoglycemia or hypoglycemia symptoms, previous problems with metformin
    a. Agrees to take metformin
        i.   Glibenclamide 2.5-5 mg → metformin 850 mg
        ii.   Glibenclamide 10 mg → metformin 850 mg + glibenclamide 2.5 mg
        iii.   Glibenclamide 15 mg → metformin 850 mg + glibenclamide 5 mg
        iv.   Glibenclamide 20 mg → metformin 850 mg + glibenclamide 10 mg
    b. Refuses to take metformin
        i.   Glibenclamide 2.5 mg → stop medications, recheck A1c in 3 months
        ii.   Glibenclamide 5 mg → glibenclamide 2.5 mg
        iii.   Glibenclamide 10 mg → glibenclamide 5 mg
        iv.   Glibenclamide 15-20 mg → glibenclamide 10 mg
10. Taking metformin and glibenclamide without problems
    a. Metformin 500-1000 mg + glibenclamide 2.5-10 mg → metformin 850 mg + current glibenclamide dose
    b. Metformin 500-1000 mg + glibenclamide 15-20 mg → metformin 850 mg + glibenclamide 10 mg
    c. Metformin 1500-2550 mg + glibenclamide 2.5-10 mg → metformin 1700 mg + current glibenclamide dose
    d. Metformin 1500-2550 mg + glibenclamide 15-20 mg → metformin 1700 mg + glibenclamide 10 mg
11. Taking metformin and glibenclamide, problems with metformin
    a. Metformin 500-850 mg + glibenclamide 2.5-10 mg, agrees to take metformin →metformin 850 mg + current glibenclamide dose
    b. Metformin 500-850 mg + glibenclamide 15-20 mg, agrees to take metformin →metformin 850 mg + glibenclamide 10 mg
    c. Metformin 500-850 mg + glibenclamide 2.5-10 mg, refuses to take metformin → current glibenclamide dose
    d. Metformin 500-850 mg + glibenclamide 15-20 mg, refuses to take metformin → glibenclamide 10 mg
    e. Metformin 1000-1700 mg + glibenclamide 2.5-10 mg → metformin 850 mg + current glibenclamide dose
    f. Metformin 1000-1700 mg + glibenclamide 15-20 mg → metformin 850 mg + glibenclamide 10 mg
    g. Metformin 2000-2550 mg + glibenclamide 2.5-10 mg → metformin 1700 mg + current glibenclamide dose
    h. Metformin 2000-2550 mg + glibenclamide 15-20 mg → metformin 1700 mg + glibenclamide 10 mg
12. Taking metformin and glibenclamide with hypoglycemia or hypoglycemia symptoms
    a. Metformin 500-1000 mg + glibenclamide 2.5 mg → metformin 850 mg
    b. Metformin 500-1000 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
    c. Metformin 500-1000 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
    d. Metformin 500-1000 mg + glibenclamide 15-20 mg → metformin 850 mg + glibenclamide 10 mg
    e. Metformin 1500-2000 mg + glibenclamide 2.5 mg → metformin 1700 mg
    f. Metformin 1500-2000 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
    g. Metformin 1500-2000 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg
    h. Metformin 1500-2000 mg + glibenclamide 15-20 mg → metformin 1700 mg + glibenclamide 10 mg
    i. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 2550 mg

56

     j.   Metformin 2550 mg + glibenclamide 5 mg → metformin 2550 mg + glibenclamide 2.5 mg
     k.   Metformin 2550 mg + glibenclamide 10 mg → metformin 2550 mg + glibenclamide 5 mg
     l.   Metformin 2550 mg + glibenclamide 15-20 mg → metformin 2550 mg + glibenclamide 10 mg

13. Taking metformin and glibenclamide, with hypoglycemia or hypoglycemia symptoms, problems with metformin
    a. Agrees to take metformin
        i.   Metformin 500-850 mg + glibenclamide 2.5 mg → metformin 850 mg
        ii.   Metformin 500-850 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
        iii.   Metformin 500-850 mg + glibenclamide 10 mg → metformin 850 mg+ glibenclamide 5 mg
        iv.   Metformin 500-850 mg + glibenclamide 15-20 mg → metformin 850 mg + glibenclamide 10 mg
    b. Refuses to take metformin
        i.   Metformin 500-850 mg + glibenclamide 2.5 mg → stop medications, recheck A1c in 3 months
        ii.   Metformin 500-850 mg + glibenclamide 5 mg → glibenclamide 2.5 mg
        iii.   Metformin 500-850 mg + glibenclamide 10 mg → glibenclamide 5 mg
        iv.   Metformin 500-850 mg + glibenclamide 15-20 mg → glibenclamide 10 mg
    c. Metformin 1000-1700 mg + glibenclamide 2.5 mg → metformin 850 mg
    d. Metformin 1000-1700 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
    e. Metformin 1000-1700 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
    f. Metformin 1000-1700 mg + glibenclamide 15-20 mg → metformin 850 mg + glibenclamide 10 mg
    g. Metformin 2000-2550 mg + glibenclamide 2.5 mg → metformin 1700 mg
    h. Metformin 2000-2550 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
    i. Metformin 2000-2550 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg
    j. Metformin 2000-2550 mg + glibenclamide 15-20 mg → metformin 1700 mg + glibenclamide 10 mg

Tx goal< A1c <9
1. Not taking medications or nonadherent, no hypoglycemia or hypoglycemia symptoms, no problems with metformin → metformin 1700 mg
2. Not taking medications or nonadherent, no hypoglycemia or hypoglycemia symptoms, problems with metformin
    a. Agrees to take metformin → metformin 850 mg + glibenclamide 2.5 mg
    b. Refuses to take metformin → glibenclamide 2.5 mg
3. Not taking medications or nonadherent, hypoglycemia or hypoglycemia symptoms → metformin 1700 mg
4. Not taking medications or nonadherent, hypoglycemia or hypoglycemia symptoms, problems with metformin
    a. Agrees to take metformin → metformin 850 mg
    b. Refuses to take metformin, prescribed glibenclamide >2.5 mg → glibenclamide 2.5 mg
    c. Refuses to take metformin, prescribed glibenclamide 2.5 mg → MD consult
5. Taking metformin without problems
    a. Metformin 500-1000 mg → metformin 1700 mg
    b. Metformin 1500-2000 mg → metformin 2550 mg
    c. Metformin 2550 mg → metformin 2550 mg + glibenclamide 2.5 mg
6. Taking metformin with problems
    a. Metformin 500-850 mg, agrees to take metformin → metformin 850 mg + glibenclamide 2.5 mg

57

      b. Metformin 500-850 mg, refuses to take metformin → glibenclamide 2.5 mg
      c. Metformin 1000-1700 mg → metformin 850 mg + glibenclamide 2.5 mg
      d. Metformin 2000-2550 mg → metformin 1700 mg + glibenclamide 2.5 mg
7. Taking glibenclamide without problems
      a. Glibenclamide 2.5-10 mg → metformin 1700 mg + glibenclamide current dose
      b. Glibenclamide 15-20 mg → metformin 1700 mg + glibenclamide 10 mg
8. Taking glibenclamide, previous problems with metformin
      a. Agrees to take metformin
          i. Glibenclamide 2.5-10 mg → metformin 850 mg + glibenclamide current dose
          ii. Glibenclamide 15-20 mg → metformin 850 mg + glibenclamide 10 mg
      b. Refuses to take metformin
          i. Glibenclamide 2.5 mg → glibenclamide 5 mg
          ii. Glibenclamide 5 mg → glibenclamide 10 mg
          iii. Glibenclamide 10-20 mg → glibenclamide 10 mg
9. Taking glibenclamide with hypoglycemia or hypoglycemia symptoms
      a. Glibenclamide 2.5 mg → metformin 1700 mg
      b. Glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
      c. Glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg
      d. Glibenclamide 15-20 mg → metformin 1700 mg + glibenclamide 10 mg
10. Taking glibenclamide with hypoglycemia or hypoglycemia symptoms, previous problems with metformin
      a. Agrees to take metformin
          i. Glibenclamide 2.5 mg → metformin 850 mg
          ii. Glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
          iii. Glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
          iv. Glibenclamide 15-20 mg → metformin 850 mg + glibenclamide 10 mg
      b. Refuses to take metformin
          i. Glibenclamide 2.5 mg → MD consult
          ii. Glibenclamide 5 mg → glibenclamide 2.5 mg
          iii. Glibenclamide 10 mg → glibenclamide 5 mg
          iv. Glibenclamide 15-20 mg → glibenclamide 10 mg
11. Taking metformin and glibenclamide without problems
      a. Metformin 500-1000 mg + glibenclamide 2.5-10 mg → metformin 1700 mg + current glibenclamide dose
      b. Metformin 500-1000 mg + glibenclamide 15-20 mg → metformin 1700 mg + glibenclamide 10 mg
      c. Metformin 1500-2000 mg + glibenclamide 2.5-10 mg → metformin 2550 mg + glibenclamide current dose
      d. Metformin 1500-2000 mg + glibenclamide 15-20 mg → metformin 2550 mg + glibenclamide 10 mg
      e. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 2550 mg + glibenclamide 5 mg
      f. Metformin 2550 mg + glibenclamide 5 mg → metformin 2550 mg + glibenclamide 10 mg
      g. Metformin 2550 mg + glibenclamide 10-20 mg → metformin 2550 mg + glibenclamide 10 mg
12. Taking metformin and glibenclamide, problems with metformin
      a. Agrees to take metformin
          i. Metformin 500-850 mg + glibenclamide 2.5 mg → metformin 850 mg + glibenclamide 5 mg
          ii. Metformin 500-850 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 10 mg

58

          iii.   Metformin 500-850 mg + glibenclamide 10-20 mg → metformin 850 mg + glibenclamide 10 mg
- b. Refuses to take metformin
    - i. Metformin 500-850 mg + glibenclamide 2.5 mg → glibenclamide 5 mg
    - ii. Metformin 500-850 mg + glibenclamide 5 mg → glibenclamide 10 mg
    - iii. Metformin 500-850 mg + glibenclamide 10-20 mg → glibenclamide 10 mg
- c. Metformin 1000-1700 mg + glibenclamide 2.5 mg → metformin 850 mg + glibenclamide 5 mg
- d. Metformin 1000-1700 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 10 mg
- e. Metformin 1000-1700 mg + glibenclamide 10-20 mg → metformin 850 mg + glibenclamide 10 mg
- f. Metformin 2000-2550 mg + glibenclamide 2.5 mg → metformin 1700 mg + glibenclamide 5 mg
- g. Metformin 2000-2550 mg + glibenclamide 5 mg→ metformin 1700 mg + glibenclamide 10 mg
- h. Metformin 2000-2550 mg + glibenclamide 10-20 mg → metformin 1700 mg + glibenclamide 10 mg

13. Taking metformin and glibenclamide with hypoglycemia or hypoglycemia symptoms
- a. Metformin 500-1000 mg + glibenclamide 2.5 mg → metformin 1700 mg
- b. Metformin 500-1000 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
- c. Metformin 500-1000 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg
- d. Metformin 500-1000 mg + glibenclamide 15-20 mg → metformin 1700 mg + glibenclamide 10 mg
- e. Metformin 1500-2000 mg + glibenclamide 2.5 mg → metformin 2550 mg
- f. Metformin 1500-2000 mg + glibenclamide 5 mg → metformin 2550 mg + glibenclamide 2.5 mg
- g. Metformin 1500-2000 mg + glibenclamide 10 mg → metformin 2550 mg + glibenclamide 5 mg
- h. Metformin 1500-2000 mg + glibenclamide 15-20 mg → metformin 2550 mg + glibenclamide 10 mg
- i. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 2550 mg
- j. Metformin 2550 mg + glibenclamide 5 mg → metformin 2550 mg + glibenclamide 2.5 mg
- k. Metformin 2550 mg + glibenclamide 10 mg → metformin 2550 mg + glibenclamide 5 mg
- l. Metformin 2550 mg + glibenclamide 15-20 mg → metformin 2550 mg + glibenclamide 10 mg

14. Taking metformin and glibenclamide, with hypoglycemia or hypoglycemia symptoms, problems with metformin
- a. Agrees to take metformin
    - i. Metformin 500-850 mg + glibenclamide 2.5 mg → metformin 850 mg
    - ii. Metformin 500-850 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
    - iii. Metformin 500-850 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
    - iv. Metformin 500-850 mg + glibenclamide 15-20 mg → metformin 850 mg + glibenclamide 10 mg
- b. Refuses to take metformin
    - i. Metformin 500-850 mg + glibenclamide 2.5 mg → MD consult
    - ii. Metformin 500-850 mg + glibenclamide 5 mg → glibenclamide 2.5 mg
    - iii. Metformin 500-850 mg + glibenclamide 10 mg → glibenclamide 5 mg
    - iv. Metformin 500-850 mg + glibenclamide 15-20 mg → glibenclamide 10 mg
- c. Metformin 1000-1700 mg + glibenclamide 2.5 mg → metformin 850 mg
- d. Metformin 1000-1700 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
- e. Metformin 1000-1700 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
- f. Metformin 1000-1700 mg + glibenclamide 15-20 mg → metformin 850 mg + glibenclamide 10 mg
- g. Metformin 2000-2550 mg + glibenclamide 2.5 mg → metformin 1700 mg

h. Metformin 2000-2550 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
i. Metformin 2000-2550 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg
j. Metformin 2000-2550 mg + glibenclamide 15-20 mg → metformin 1700 mg + glibenclamide 10 mg

9≤ A1c ≤14
1. Not taking medications → metformin 1700 mg + glibenclamide 2.5 mg
2. Not taking medications, problems with metformin
    a. Agrees to take metformin → metformin 850 mg + glibenclamide 2.5 mg
    b. Refuses to take metformin → glibenclamide 2.5 mg
3. Not taking medications, hypoglycemia or hypoglycemia symptoms → metformin 1700 mg
4. Not taking medications, hypoglycemia or hypoglycemia symptoms, problems with metformin
    a. Agrees to take metformin, prescribed glibenclamide >2.5 mg → metformin 850 mg + glibenclamide 2.5 mg
    b. Agrees to take metformin, prescribed glibenclamide 2.5 mg → metformin 850 mg
    c. Refuses to take metformin, prescribed glibenclamide >2.5 mg → glibenclamide 2.5 mg
    d. Refuses to take metformin, prescribed glibenclamide 2.5 mg → MD consult
5. Taking metformin without problems
    a. Metformin 500-2000 mg → metformin 1700 mg + glibenclamide 2.5 mg
    b. Metformin 2550 mg → metformin 2550 mg + glibenclamide 2.5 mg
6. Taking metformin with problems
    a. Metformin 500-850 mg, agrees to take metformin → metformin 850 mg + glibenclamide 2.5 mg
    b. Metformin 500-850 mg, refuses to take metformin → glibenclamide 2.5 mg
    c. Metformin 1000-1700 mg → metformin 850 mg + glibenclamide 2.5 mg
    d. Metformin 2000-2550 mg → metformin 1700 mg + glibenclamide 2.5 mg
7. Taking glibenclamide without problems
    a. Glibenclamide 2.5-10 mg → metformin 1700 mg +glibenclamide current dose
    b. Glibenclamide 15-20 mg → metformin 1700 mg + glibenclamide 10 mg
8. Taking glibenclamide without problems, previous problems with metformin
    a. Agrees to take metformin
        i. Glibenclamide 2.5-10 mg → metformin 850 mg + glibenclamide current dose
        ii. Glibenclamide 15-20 mg → metformin 850 mg + glibenclamide 10 mg
    b. Refuses to take metformin
        i. Glibenclamide 2.5 mg → glibenclamide 5 mg
        ii. Glibenclamide 5 mg → glibenclamide 10 mg
        iii. Glibenclamide 10-20 mg → glibenclamide 10 mg
9. Taking glibenclamide with hypoglycemia or hypoglycemia symptoms
    a. Glibenclamide 2.5 mg → metformin 1700 mg
    b. Glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
    c. Glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg
    d. Glibenclamide 15-20 mg → metformin 1700 mg + glibenclamide 10 mg
10. Taking glibenclamide with hypoglycemia or hypoglycemia symptoms, previous problems with metformin
    a. Agrees to take metformin
        i. Glibenclamide 2.5 mg → metformin 850 mg
        ii. Glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
        iii. Glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
        iv. Glibenclamide 15-20 mg → metformin 850 mg + glibenclamide 10 mg

60

      b. Refuses to take metformin
- i. Glibenclamide 2.5 mg →MD consult
- ii. Glibenclamide 5 mg → glibenclamide 2.5 mg
- iii. Glibenclamide 10 mg → glibenclamide 5 mg
- iv. Glibenclamide 15-20 mg → glibenclamide 10 mg

11. Taking metformin and glibenclamide without problems
- a. Metformin 500-1000 mg + glibenclamide 2.5-10 mg → metformin 1700 mg + current glibenclamide dose
- b. Metformin 500-1000 mg + glibenclamide 15-20 mg → metformin 1700 mg + glibenclamide 10 mg
- c. Metformin 1500-2000 mg + glibenclamide 2.5-10 mg → metformin 2550 mg + glibenclamide current dose
- d. Metformin 1500-2000 mg + glibenclamide 15-20 mg → metformin 2550 mg + glibenclamide current dose
- e. Metformin 2550 mg + glibenclamide 2.5-10 mg → metformin 2550 mg + glibenclamide current dose
- f. Metformin 2550 mg + glibenclamide 15-20 mg → metformin 2550 mg + glibenclamide 10 mg

12. Taking metformin and glibenclamide, problems with metformin
- a. Agrees to take metformin
  - i. Metformin 500-850 mg + glibenclamide 2.5 mg → metformin 850 mg + glibenclamide 5 mg
  - ii. Metformin 500-850 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 10 mg
  - iii. Metformin 500-850 mg + glibenclamide 10-20 mg → metformin 850 mg + glibenclamide 10 mg
- b. Refuses to take metformin
  - i. Metformin 500-850 mg + glibenclamide 2.5 mg → glibenclamide 5 mg
  - ii. Metformin 500-850 mg + glibenclamide 5 mg → glibenclamide 10 mg
  - iii. Metformin 500-850 mg + glibenclamide 10-20 mg → glibenclamide 10 mg
- c. Metformin 1000-1700 mg + glibenclamide 2.5 mg → metformin 850 mg + glibenclamide 5 mg
- d. Metformin 1000-1700 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 10 mg
- e. Metformin 1000-1700 mg + glibenclamide 10-20 mg → metformin 850 mg + glibenclamide 10 mg
- f. Metformin 2000-2550 mg + glibenclamide 2.5 mg → metformin 1700 mg + glibenclamide 5 mg
- g. Metformin 2000-2550 mg + glibenclamide 5 mg→ metformin 1700 mg + glibenclamide 10 mg
- h. Metformin 2000-2550 mg + glibenclamide 10-20 mg → metformin 1700 mg + glibenclamide 10 mg

13. Taking metformin and glibenclamide with hypoglycemia or hypoglycemia symptoms
- a. Metformin 500-1000 mg + glibenclamide 2.5 mg → metformin 1700 mg
- b. Metformin 500-1000 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
- c. Metformin 500-1000 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg
- d. Metformin 500-1000 mg + glibenclamide 15-20 mg → metformin 1700 mg + glibenclamide 10 mg
- e. Metformin 1500-2000 mg + glibenclamide 2.5 mg → metformin 2550 mg
- f. Metformin 1500-2000 mg + glibenclamide 5 mg → metformin 2550 mg + glibenclamide 2.5 mg
- g. Metformin 1500-2000 mg + glibenclamide 10 mg → metformin 2550 mg + glibenclamide 5 mg
- h. Metformin 1500-2000 mg + glibenclamide 15-20 mg → metformin 2550 mg + glibenclamide 10 mg
- i. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 2550 mg
- j. Metformin 2550 mg + glibenclamide 5 mg → metformin 2550 mg + glibenclamide 2.5 mg

      k. Metformin 2550 mg + glibenclamide 10 mg → metformin 2550 mg + glibenclamide 5 mg
      l. Metformin 2550 mg + glibenclamide 15-20 mg → metformin 2550 mg + glibenclamide 10 mg

14. Taking metformin and glibenclamide, with hypoglycemia or hypoglycemia symptoms, problems with metformin

    a. Agrees to take metformin
       i. Metformin 500-850 mg + glibenclamide 2.5 mg → metformin 850 mg
       ii. Metformin 500-850 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
       iii. Metformin 500-850 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
       iv. Metformin 500-850 mg + glibenclamide 15-20 mg → metformin 850 mg + glibenclamide 10 mg
    b. Refuses to take metformin
       i. Metformin 500-850 mg + glibenclamide 2.5 mg → MD consult
       ii. Metformin 500-850 mg + glibenclamide 5 mg → glibenclamide 2.5 mg
       iii. Metformin 500-850 mg + glibenclamide 10 mg → glibenclamide 5 mg
       iv. Metformin 500-850 mg + glibenclamide 15-20 mg → glibenclamide 10 mg
    c. Metformin 1000-1700 mg + glibenclamide 2.5 mg → metformin 850 mg
    d. Metformin 1000-1700 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
    e. Metformin 1000-1700 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
    f. Metformin 1000-1700 mg + glibenclamide 15-20 mg → metformin 850 mg + glibenclamide 10 mg
    g. Metformin 2000-2550 mg + glibenclamide 2.5 mg → metformin 1700 mg
    h. Metformin 2000-2550 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
    i. Metformin 2000-2550 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg
    j. Metformin 2000-2550 mg + glibenclamide 15-20 mg → metformin 1700 mg + glibenclamide 10 mg

A1c >14 OR FBG >400
- Coordinator/MD consult for all cases

Appendix 9 - Medication Instructions

Metformin 850 mg[50]
- For patients starting metformin
  - Start taking one 850 mg tablet with breakfast
  - After two weeks, start taking two tablets daily, one with breakfast and one with dinner
- Dosing
  - 850 mg → take one tablet per day with breakfast
  - 1700 mg → take two tablets daily, one with breakfast and one with dinner
  - 2550 mg → take three tablets daily, one with breakfast, one with lunch, and one with dinner
- Guidance for patients experiencing metformin GI side effects
  - Always take metformin with food
  - Try taking metformin at night, instead of in the morning
  - Take half a tablet with breakfast and half a tablet with dinner (for patients taking one tablet per day)

Version #: 1.0

Glibenclamide 5 mg[68]
- Guidance for all patients → Take with breakfast or the main meal of the day at the same time each day. **Should only be taken with food. Do not take on days that you are fasting, not able to eat, or if you will be eating significantly less food than you normally eat.**
- Dosing
  - 2.5 mg (starting dose) → Take ½ tablet (2.5 mg) once daily with breakfast or the first main meal of the day
  - 5 mg → take one tablet once daily with breakfast or the first main meal of the day
  - 10 mg → take two tablets daily with breakfast or the first main meal of the day

Hypoglycemia teaching for patients taking glibenclamide[69]
- Glibenclamide can cause low blood sugar, which sometimes can be dangerous
- Low blood sugar can cause symptoms such as shaking/tremors, feeling confused, feeling uncoordinated, sweating a lot more than normal, feeling very anxious for no reason, or heart beating fast or irregular. These usually come on suddenly and happen when you haven't eaten for a while, when doing hard physical work or exercising, or while drinking alcohol.
- How to avoid low blood sugar
  - Eat regular meals
  - Take glibenclamide with the first main meal of the day and try to take at the same time each day. Do not taking if you will be fasting, not able to eat, or eating a lot less than you normally do.
  - Eat a snack with carbohydrates before doing hard physical work or exercising
  - Avoid drinking alcohol
- If you think your blood sugar is low, you should eat or drink one of the following items:
  - 1 tablespoon of sugar
  - 6 hard candies
  - 2 tablespoons of raisins
  - 1 tablespoon of honey
  - ½ cup of fruit juice
  - 1 cup of skim milk
  - ½ cup of regular soda (not diet soda)
- You should have at least one of these items with you when you leave the house so you can treat symptoms if you need to
- Sometimes, a person with very low blood sugar becomes so confused or sleepy that they can't eat or drink anything. Teach your family that if this happens to you, they should sprinkle sugar under your tongue and call for an ambulance right away.
- Let your health promoter know if you are having symptoms of low blood sugar and if these get better when you eat or drink something with sugar. If someone had to help you because you were very sleepy or confused, you should get help right away. You should not take your glibenclamide again until you see your health promoter.

Appendix 10 - Monthly Medication Dosing Recommendations

Version #: 1.0

FBG <80 (<90)[18] or PPBG<130(150)

1. Metformin without problems, adherent → continue current doses
2. Metformin without problems, nonadherent
   a. Metformin 850 mg → metformin 850 mg
   b. Metformin 1700-2550 mg → metformin 1700 mg
3. Metformin with problems, adherent
   a. Metformin 850 mg, willing to continue → Metformin 850 mg
   b. Metformin 850 mg, not willing to continue → stop medications, check A1c when next indicated
   c. Metformin 1700 mg → metformin 850 mg
   d. Metformin 2550 mg → metformin 1700 mg
4. Metformin with problems, nonadherent → same as #3
5. Glibenclamide without problems, no previous problems with metformin, took yesterday → metformin 1700 mg
6. Glibenclamide without problems, no previous problems with metformin, did not take yesterday → metformin 1700 mg
7. Glibenclamide without problems, previous problems with metformin, took yesterday
   a. Agrees to take metformin
      i. Glibenclamide 2.5-5 mg → metformin 850 mg
      ii. Glibenclamide 10 mg → metformin 850 mg + glibenclamide 2.5 mg
   b. Refuses to take metformin
      i. Glibenclamide 2.5 mg → stop medications, recheck A1c in 3 months
      ii. Glibenclamide 5 mg → glibenclamide 2.5 mg
      iii. Glibenclamide 10 mg → glibenclamide 5 mg
8. Glibenclamide without problems, previous problems with metformin, did not take yesterday
   a. Agrees to take metformin → metformin 850 mg
   b. Refuses to take metformin → stop medications, recheck A1c in 3 months
9. Glibenclamide with hypoglycemia or hypoglycemia symptoms, no previous problems with metformin, took yesterday → metformin 1700 mg
10. Glibenclamide with hypoglycemia or hypoglycemia symptoms, no previous problems with metformin, did not take yesterday → metformin 1700 mg
11. Glibenclamide with hypoglycemia or hypoglycemia symptoms, previous problems with metformin, took yesterday → same as #8
12. Glibenclamide with hypoglycemia or hypoglycemia symptoms, previous problems with metformin did not take yesterday → same as #8
13. Metformin and glibenclamide without problems, adherent, took glibenclamide yesterday
    a. Metformin 850 mg + glibenclamide any dose → metformin 1700 mg
    b. Metformin 1700-2550 mg + glibenclamide 2.5 mg → metformin 1700 mg
    c. Metformin 1700-2550 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
    d. Metformin 1700-2550 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg
14. Metformin and glibenclamide without problems, nonadherent, took glibenclamide yesterday → same as #13
15. Metformin and glibenclamide without problems, adherent, did not take glibenclamide yesterday → metformin 1700 mg

---

[18] Numbers in parentheses refer to the relevant measurements for patients who have relaxed glycemic goals (A1c ≤8, FBG 90-150, PPBG <200)

Version #: 1.0

16. Metformin and glibenclamide without problems, nonadherent, did not take glibenclamide yesterday → metformin 1700 mg
17. Metformin and glibenclamide, problems with metformin, adherent, took glibenclamide yesterday
    a. Agrees to take metformin
        i. Metformin 850 mg + glibenclamide 2.5mg → metformin 850 mg
        ii. Metformin 850 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
        iii. Metformin 850 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
    b. Refuses to take metformin
        i. Metformin 850 mg + glibenclamide 2.5 mg → stop medications, recheck A1c in 3 months
        ii. Metformin 850 mg + glibenclamide 5 mg → glibenclamide 2.5 mg
        iii. Metformin 850 mg + glibenclamide 10 mg → glibenclamide 5 mg
    c. Metformin 1700 mg + glibenclamide 2.5 mg → metformin 850 mg
    d. Metformin 1700 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5
    e. Metformin 1700 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
    f. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 1700 mg
    g. Metformin 2550 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
    h. Metformin 2550 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg
18. Metformin and glibenclamide, problems with metformin, nonadherent, took glibenclamide yesterday → same as #17
19. Metformin and glibenclamide, problems with metformin, adherent, did not take glibenclamide yesterday
    a. Metformin 850 mg + glibenclamide any dose, agrees to take metformin → metformin 850 mg
    b. Metformin 850 mg + glibenclamide any dose, refuses to take metformin → stop medications, recheck A1c in 3 months
    c. Metformin 1700 mg + glibenclamide any dose → metformin 850 mg
    d. Metformin 2550 mg + glibenclamide any dose → metformin 1700 mg
20. Metformin and glibenclamide, problems with metformin, nonadherent, did not take glibenclamide yesterday → same as #19
21. Metformin and glibenclamide, hypoglycemia or hypoglycemia symptoms, adherent, took glibenclamide yesterday
    a. Metformin 850 mg + glibenclamide any dose → metformin 1700 mg
    b. Metformin 1700 mg + glibenclamide 2.5-5 mg → metformin 1700 mg
    c. Metformin 1700 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 2.5 mg
    d. Metformin 2550 mg + glibenclamide 2.5-5 mg → metformin 2550 mg
    e. Metformin 2550 mg + glibenclamide 10 mg → metformin 2550 mg + glibenclamide 5 mg
22. Metformin and glibenclamide, hypoglycemia or hypoglycemia symptoms, nonadherent, took glibenclamide yesterday
    a. Metformin 850 mg + glibenclamide any dose → metformin 1700 mg
    b. Metformin 1700-2500 mg + glibenclamide 2.5-5 mg → metformin 1700 mg
    c. Metformin 1700-2550 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 2.5 mg
23. Metformin and glibenclamide, hypoglycemia or hypoglycemia symptoms, adherent, did not take glibenclamide yesterday
    a. Metformin 850-1700 mg + glibenclamide any dose → metformin 1700 mg
    b. Metformin 2550 mg + glibenclamide any dose → metformin 2550 mg
24. Metformin and glibenclamide, hypoglycemia or hypoglycemia symptoms, nonadherent, did not take glibenclamide yesterday → metformin 1700 mg
25. Metformin and glibenclamide, problems with metformin, hypoglycemia or hypoglycemia symptoms, adherent, took glibenclamide yesterday

    a. Agrees to take metformin
        i. Metformin 850 mg + glibenclamide 2.5-5 mg → metformin 850 mg
        ii. Metformin 850 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 2.5 mg
    b. Refuses to take metformin
        i. Metformin 850 mg + glibenclamide 2.5-5 mg → stop medications, recheck A1c in 3 months
        ii. Metformin 850 mg + glibenclamide 10 mg → glibenclamide 2.5 mg
    c. Metformin 1700 mg + glibenclamide 2.5-5 mg → metformin 850 mg
    d. Metformin 1700 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 2.5 mg
    e. Metformin 2550 mg + glibenclamide 2.5-5 mg → metformin 1700 mg
    f. Metformin 2550 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 2.5 mg

26. Metformin and glibenclamide, problems with metformin, hypoglycemia or hypoglycemia symptoms, nonadherent, took glibenclamide yesterday → same as #25
27. Metformin and glibenclamide, problems with metformin, hypoglycemia or hypoglycemia symptoms, adherent, did not take glibenclamide yesterday
    a. Metformin 850 mg + glibenclamide any dose, agrees to take metformin → metformin 850 mg
    b. Metformin 850 mg + glibenclamide any dose, refuses to take metformin → stop medications, recheck A1c in 3 months
    c. Metformin 1700 mg + glibenclamide any dose → metformin 850 mg
    d. Metformin 2550 mg + glibenclamide any dose → metformin 1700 mg
28. Metformin and glibenclamide, problems with metformin, hypoglycemia or hypoglycemia symptoms, nonadherent, did not take glibenclamide yesterday → same as #27

80(90)≤FBG≤130(150) or 130(150)≤PPBG<180(200)
1. Metformin without problems, adherent → continue current doses
2. Metformin without problems, nonadherent
    a. Metformin 850 mg → metformin 850 mg
    b. Metformin 1700-2550 mg → metformin 1700 mg
3. Metformin with problems, adherent
    a. Metformin 850 mg, willing to continue → Metformin 850 mg
    b. Metformin 850 mg, not willing to continue → stop medications, check A1c when next indicated
    c. Metformin 1700 mg → metformin 850 mg
    d. Metformin 2550 mg → metformin 1700 mg
4. Metformin with problems, nonadherent → same as #3
5. Glibenclamide without problems, no previous problems with metformin, took yesterday → continue current dose
6. Glibenclamide without problems, no previous problems with metformin, did not take yesterday → metformin 1700 mg
7. Glibenclamide without problems, previous problems with metformin, took yesterday → continue current dose
8. Glibenclamide without problems, previous problems with metformin, did not take yesterday
    a. Agrees to take metformin → metformin 850 mg
    b. Refuses to take metformin
        i. Glibenclamide 2.5 mg → stop medications, recheck A1c when next indicated
        ii. Glibenclamide 5 mg → glibenclamide 2.5 mg
        iii. Glibenclamide 10 mg → glibenclamide 5 mg
9. Glibenclamide with hypoglycemia symptoms, no previous problems with metformin, took yesterday

      a. Glibenclamide 2.5-5 mg → metformin 1700 mg
      b. Glibenclamide 10 mg → metformin 1700 mg + glibenclamide 2.5 mg

10. Glibenclamide with hypoglycemia or hypoglycemia symptoms, no previous problems with metformin, did not take yesterday → metformin 1700 mg

11. Glibenclamide with hypoglycemia symptoms, previous problems with metformin, took yesterday
      a. Agrees to take metformin
            i. Glibenclamide 2.5-5 mg → metformin 850 mg
            ii. Glibenclamide 10 mg → metformin 850 mg + glibenclamide 2.5 mg
      b. Refuses to take metformin
            i. Glibenclamide 2.5 mg → stop medications, check A1c when next indicated
            ii. Glibenclamide 5 mg → glibenclamide 2.5 mg
            iii. Glibenclamide 10 mg → glibenclamide 5 mg

12. Glibenclamide with hypoglycemia symptoms, previous problems with metformin did not take yesterday
      a. Agrees to take metformin → metformin 850 mg
      b. Refuses to take metformin
            i. Glibenclamide 2.5-5 mg → stop medications, check A1c when next indicated
            ii. Glibenclamide 10 mg → glibenclamide 2.5 mg

13. Metformin and glibenclamide without problems, adherent, took glibenclamide yesterday → continue current doses

14. Metformin and glibenclamide without problems, nonadherent, took glibenclamide yesterday
      a. Metformin any dose + glibenclamide 2.5 mg → metformin 1700 mg
      b. Metformin any dose + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
      c. Metformin any dose + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg

15. Metformin and glibenclamide without problems, adherent, did not take glibenclamide yesterday
      a. Metformin any dose + glibenclamide 2.5mg → metformin current dose
      b. Metformin any dose + glibenclamide 5 mg → metformin current dose + glibenclamide 2.5 mg
      c. Metformin any dose + glibenclamide 10 mg → metformin current dose + glibenclamide 5 mg

16. Metformin and glibenclamide without problems, nonadherent, did not take glibenclamide yesterday
      a. Metformin all doses + glibenclamide 2.5-5 mg → metformin 1700 mg
      b. Metformin all doses + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 2.5 mg

17. Metformin and glibenclamide, problems with metformin, adherent, took glibenclamide yesterday
      a. Metformin 850 mg + any dose of glibenclamide, agrees to take metformin → continue current doses
      b. Metformin 850 mg + any dose of glibenclamide, refuses to take metformin → continue current dose of glibenclamide
      c. Metformin 1700 mg + glibenclamide any dose → metformin 850 mg + glibenclamide current dose
      d. Metformin 2550 mg + glibenclamide any dose → metformin 1700 mg + glibenclamide current dose

18. Metformin and glibenclamide, problems with metformin, nonadherent, took glibenclamide yesterday → same as #17

19. Metformin and glibenclamide, problems with metformin, adherent, did not take glibenclamide yesterday
      a. Agrees to take metformin
            i. Metformin 850 mg + glibenclamide 2.5 mg → metformin 850 mg
            ii. Metformin 850 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
            iii. Metformin 850 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
      b. Refuses to take metformin

67

       i. Metformin 850 mg + glibenclamide 2.5 mg → stop medications, check A1c when next indicated
       ii. Metformin 850 mg + glibenclamide 5 mg → glibenclamide 2.5 mg
       iii. Metformin 850 mg + glibenclamide 10 mg → glibenclamide 5 mg
   c. Metformin 1700 mg + glibenclamide 2.5 mg → metformin 850 mg
   d. Metformin 1700 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
   e. Metformin 1700 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
   f. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 1700 mg
   g. Metformin 2550 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
   h. Metformin 2550 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg

20. Metformin and glibenclamide, problems with metformin, nonadherent, did not take glibenclamide yesterday
   a. Metformin 850 mg + glibenclamide any dose, agrees to take metformin → metformin 850 mg
   b. Refuses to take metformin
       i. Metformin 850 mg + glibenclamide 2.5-5 mg → stop medications, recheck A1c in 3 months
       ii. Metformin 850 mg + glibenclamide 10 mg → glibenclamide 2.5 mg
   c. Metformin 1700 mg + glibenclamide 2.5-5 mg → metformin 850 mg
   d. Metformin 1700 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 2.5 mg
   e. Metformin 2550 mg + glibenclamide 2.5-5 mg → metformin 1700 mg
   f. Metformin 2550 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 2.5 mg

21. Metformin and glibenclamide, hypoglycemia symptoms, adherent, took glibenclamide yesterday
   a. Metformin 850 mg + glibenclamide 2.5 mg → metformin 1700 mg
   b. Metformin 850 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
   c. Metformin 850 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg
   d. Metformin 1700 mg + glibenclamide 2.5 mg → metformin 1700 mg
   e. Metformin 1700 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
   f. Metformin 1700 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg
   g. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 2550 mg
   h. Metformin 2550 mg + glibenclamide 5 mg → metformin 2550 mg + glibenclamide 2.5 mg
   i. Metformin 2550 mg + glibenclamide 10 mg → metformin 2550 mg + glibenclamide 5 mg

22. Metformin and glibenclamide, hypoglycemia symptoms, nonadherent, took glibenclamide yesterday
   a. Metformin 850 mg + glibenclamide 2.5 mg → metformin 1700 mg
   b. Metformin 850 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
   c. Metformin 850 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg
   d. Metformin 1700-2550 mg + glibenclamide 2.5 mg → metformin 1700 mg
   e. Metformin 1700-2550 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
   f. Metformin 1700-2550 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg

23. Metformin and glibenclamide, hypoglycemia symptoms, adherent, did not take glibenclamide yesterday
   a. Metformin 850-1700 mg + glibenclamide any dose → metformin 1700 mg
   b. Metformin 2550 mg + glibenclamide any dose → metformin 2550 mg

24. Metformin and glibenclamide, hypoglycemia symptoms, nonadherent, did not take glibenclamide yesterday → metformin 1700 mg

25. Metformin and glibenclamide, problems with metformin, hypoglycemia symptoms, adherent, took glibenclamide yesterday
   a. Agrees to take metformin
       i. Metformin 850 mg + glibenclamide 2.5 mg → metformin 850 mg

      ii.   Metformin 850 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
      iii.   Metformin 850 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
  b. Refuses to take metformin
      i.   Metformin 850 mg + glibenclamide 2.5 mg → stop medications, recheck A1c when next indicated
      ii.   Metformin 850 mg + glibenclamide 5 mg → glibenclamide 2.5 mg
      iii. Metformin 850 mg + glibenclamide 10 mg → glibenclamide 5 mg
  c. Metformin 1700 mg + glibenclamide 2.5 mg → metformin 850 mg
  d. Metformin 1700 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
  e. Metformin 1700 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
  f. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 1700 mg
  g. Metformin 2550 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
  h. Metformin 2550 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg

26. Metformin and glibenclamide, problems with metformin, hypoglycemia symptoms, nonadherent, took glibenclamide yesterday → same as #25

27. Metformin and glibenclamide, problems with metformin, hypoglycemia symptoms, adherent, did not take glibenclamide yesterday
  a. Taking metformin 850 mg + glibenclamide any dose, agrees to take metformin → metformin 850 mg
  b. Refuses to take metformin
      i.   Metformin 850 mg + glibenclamide 2.5-5 mg → Stop medications, recheck A1c when next indicated
      ii.   Metformin 850 mg + glibenclamide 10 mg → glibenclamide 2.5 mg
  c. Metformin 1700 mg + glibenclamide any dose → metformin 850 mg
  d. Metformin 2550 mg + glibenclamide any dose → metformin 1700 mg

28. Metformin and glibenclamide, problems with metformin, hypoglycemia or hypoglycemia symptoms, nonadherent, did not take glibenclamide yesterday → same as #27

130(150)<FBG<180(200) or 180(200)≤PPBG<300
1. Metformin without problems, adherent → continue current doses
2. Metformin without problems, nonadherent → continue current doses
3. Metformin with problems, adherent
  a. Metformin 850 mg, willing to continue → Metformin 850 mg
  b. Metformin 850 mg, not willing to continue → glibenclamide 2.5 mg
  c. Metformin 1700 mg → metformin 850 mg + glibenclamide 2.5 mg
  d. Metformin 2550 mg → metformin 1700 mg + glibenclamide 2.5 mg
4. Metformin with problems, nonadherent
  a. Metformin 850 mg, willing to continue → metformin 850 mg
  b. Metformin 850 mg, not willing to continue → glibenclamide 2.5 mg
  c. Metformin 1700 mg → metformin 850 mg
  d. Metformin 2550 mg → metformin 1700 mg
5. Glibenclamide without problems, no previous problems with metformin, took yesterday → continue current dose
6. Glibenclamide without problems, no previous problems with metformin, did not take yesterday → continue current dose
7. Glibenclamide without problems, previous problems with metformin, took yesterday → continue current dose

Version #: 1.0

8. Glibenclamide without problems, previous problems with metformin, did not take yesterday → continue current dose
9. Glibenclamide with hypoglycemia symptoms, no previous problems with metformin, took yesterday
    a. Glibenclamide 2.5 mg → metformin 1700 mg
    b. Glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
    c. Glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg
10. Glibenclamide with hypoglycemia or hypoglycemia symptoms, no previous problems with metformin, did not take yesterday
    a. Glibenclamide 2.5-5 mg → metformin 1700 mg
    b. Glibenclamide 10 mg → metformin 1700 mg + glibenclamide 2.5 mg
11. Glibenclamide with hypoglycemia symptoms, previous problems with metformin, took yesterday
    a. Agrees to take metformin
        i.   Glibenclamide 2.5 mg → metformin 850 mg
        ii. Glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
        iii. Glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
    b. Refuses to take metformin
        i.   Glibenclamide 2.5 mg → MD consult
        ii. Glibenclamide 5 mg → glibenclamide 2.5 mg
        iii. Glibenclamide 10 mg → glibenclamide 5 mg
12. Glibenclamide with hypoglycemia symptoms, previous problems with metformin, did not take yesterday
    a. Agrees to take metformin
        i.   Glibenclamide 2.5-5 mg → metformin 850 mg
        ii. Glibenclamide 10 mg → metformin 850 mg + glibenclamide 2.5 mg
    b. Refuses to take metformin
        i.   Glibenclamide 2.5 mg → MD consult
        ii. Glibenclamide 5 mg → glibenclamide 2.5 mg
        iii. Glibenclamide 10 mg → glibenclamide 5 mg
13. Metformin and glibenclamide without problems, adherent, took glibenclamide yesterday → continue current doses
14. Metformin and glibenclamide without problems, nonadherent, took glibenclamide yesterday → continue current doses
15. Metformin and glibenclamide without problems, adherent, did not take glibenclamide yesterday → continue current doses
16. Metformin and glibenclamide without problems, nonadherent, did not take glibenclamide yesterday
    a. Metformin all doses + glibenclamide 2.5mg → metformin current dose
    b. Metformin all doses + glibenclamide 5 mg → metformin current dose + glibenclamide 2.5 mg
    c. Metformin all doses + glibenclamide 10 mg → metformin current dose + glibenclamide 5 mg
17. Metformin and glibenclamide, problems with metformin, adherent, took glibenclamide yesterday
    a. Metformin 850 mg + any dose of glibenclamide, agrees to take metformin → continue current doses
    b. Refuses to take metformin
        i.   Metformin 850 mg + glibenclamide 2.5 mg → glibenclamide 5 mg
        ii. Metformin 850mg + glibenclamide 5-10 mg → glibenclamide 10 mg
    c. Metformin 1700 mg + glibenclamide 2.5 mg → metformin 850 mg + glibenclamide 5 mg
    d. Metformin 1700 mg + glibenclamide 5-10 mg → metformin 850 mg + glibenclamide 10 mg
    e. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 1700 mg + glibenclamide 5 mg
    f. Metformin 2550 mg + glibenclamide 5-10 mg → metformin 1700 mg + glibenclamide 10 mg

70

18. Metformin and glibenclamide, problems with metformin, nonadherent, took glibenclamide yesterday
    a. Metformin 850 mg + any dose of glibenclamide, agrees to take metformin → continue current doses
    b. Refuses to take metformin → stop metformin, continue current dose of glibenclamide
    c. Metformin 1700 mg + glibenclamide any dose → metformin 850 mg + glibenclamide current dose
    d. Metformin 2550 mg + glibenclamide any dose → metformin 1700 mg + glibenclamide current dose
19. Metformin and glibenclamide, problems with metformin, adherent, did not take glibenclamide yesterday → same as #18
20. Metformin and glibenclamide, problems with metformin, nonadherent, did not take glibenclamide yesterday
    a. Agrees to take metformin
        i. Metformin 850 mg + glibenclamide 2.5 mg → metformin 850 mg
        ii. Metformin 850 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
        iii. Metformin 850 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
    b. Metformin 850 mg + glibenclamide any dose, refuses to take metformin → continue current dose of glibenclamide
    c. Metformin 1700 mg + glibenclamide 2.5 mg → metformin 850 mg
    d. Metformin 1700 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
    e. Metformin 1700 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
    f. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 1700 mg
    g. Metformin 2550 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
    h. Metformin 2550 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg
21. Metformin and glibenclamide, hypoglycemia symptoms, adherent, took glibenclamide yesterday
    a. Metformin 850 mg + glibenclamide 2.5 mg → metformin 1700 mg
    b. Metformin 850 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
    c. Metformin 850 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg
    d. Metformin 1700 mg + glibenclamide 2.5 mg → metformin 2550 mg
    e. Metformin 1700 mg + glibenclamide 5 mg → metformin 2550 mg + glibenclamide 2.5 mg
    f. Metformin 1700 mg + glibenclamide 10 mg → metformin 2550 mg + glibenclamide 5 mg
    g. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 2550 mg
    h. Metformin 2550 mg + glibenclamide 5 mg → metformin 2550 mg + glibenclamide 2.5 mg
    i. Metformin 2550 mg + glibenclamide 10 mg → metformin 2550 mg + glibenclamide 5 mg
22. Metformin and glibenclamide, hypoglycemia symptoms, nonadherent, took glibenclamide yesterday → same as #16
23. Metformin and glibenclamide, hypoglycemia symptoms, adherent, did not take glibenclamide yesterday → same as #16
24. Metformin and glibenclamide, hypoglycemia symptoms, nonadherent, did not take glibenclamide yesterday
    a. Metformin all doses + glibenclamide 2.5-5 mg → metformin current dose
    b. Metformin all doses + glibenclamide 10 mg → metformin current dose + glibenclamide 2.5 mg
25. Metformin and glibenclamide, problems with metformin, hypoglycemia symptoms, adherent, took glibenclamide yesterday
    a. Agrees to take metformin
        i. Metformin 850 mg + glibenclamide 2.5 mg → metformin 850 mg
        ii. Metformin 850 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
        iii. Metformin 850 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg

71

   b. Refuses to take metformin
     i. Metformin 850 mg + glibenclamide 2.5 mg → MD consult
     ii. Metformin 850 mg + glibenclamide 5 mg → glibenclamide 2.5 mg
     iii. Metformin 850 mg + glibenclamide 10 mg → glibenclamide 5 mg
   c. Metformin 1700 mg + glibenclamide 2.5 mg → metformin 850 mg
   d. Metformin 1700 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
   e. Metformin 1700 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
   f. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 1700 mg
   g. Metformin 2550 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
   h. Metformin 2550 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg

26. Metformin and glibenclamide, problems with metformin, hypoglycemia symptoms, nonadherent, took glibenclamide yesterday → same as #25
27. Metformin and glibenclamide, problems with metformin, hypoglycemia symptoms, adherent, did not take glibenclamide yesterday
   a. Agrees to take metformin
     i. Metformin 850 mg + glibenclamide 2.5-5 mg → metformin 850 mg
     ii. Metformin 850 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 2.5 mg
   b. Refuses to take metformin
     i. Metformin 850 mg + glibenclamide 2.5-5 mg → MD consult
     ii. Metformin 850 mg + glibenclamide 10 mg → glibenclamide 2.5 mg
   c. Metformin 1700 mg + glibenclamide 2.5-5 mg → metformin 850 mg
   d. Metformin 1700 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 2.5 mg
   e. Metformin 2550 mg + glibenclamide 2.5-5 mg → metformin 1700 mg
   f. Metformin 2550 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 2.5 mg
28. Metformin and glibenclamide, problems with metformin, hypoglycemia or hypoglycemia symptoms, nonadherent, did not take glibenclamide yesterday → same as #27

180(200)≤FBG<400 or 300≤PPBG<HI
1. Metformin without problems, adherent
   a. Metformin 850 mg → metformin 1700 mg
   b. Metformin 1700 mg → metformin 2550 mg
   c. Metformin 2550 mg → metformin 2550 mg + glibenclamide 2.5 mg
2. Metformin without problems, nonadherent → continue current doses
3. Metformin with problems, adherent
   a. Metformin 850 mg, willing to continue → metformin 850 mg + glibenclamide 2.5 mg
   b. Metformin 850 mg, not willing to continue → glibenclamide 2.5 mg
   c. Metformin 1700 mg → metformin 850 mg + glibenclamide 2.5 mg
   d. Metformin 2550 mg → metformin 1700 mg + glibenclamide 2.5 mg
4. Metformin with problems, nonadherent → same as #3
5. Glibenclamide without problems, no previous problems with metformin, took yesterday
   a. Glibenclamide 2.5 mg → metformin 1700 mg + glibenclamide 2.5 mg
   b. Glibenclamide 5 mg → metformin 1700 mg + glibenclamide 5 mg
   c. Glibenclamide 10 mg → metformin 1700 mg + glibenclamide 10 mg
6. Glibenclamide without problems, no previous problems with metformin, did not take yesterday
   a. Glibenclamide 2.5 mg → metformin 1700 mg
   b. Glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
   c. Glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg

72

7. Glibenclamide without problems, previous problems with metformin, took yesterday
   a. Agrees to take metformin → metformin 850 mg + current glibenclamide dose
   b. Refuses to take metformin
      i. Glibenclamide 2.5 mg → glibenclamide 5 mg
      ii. Glibenclamide 5 mg → glibenclamide 10 mg
      iii. Glibenclamide 10 mg → glibenclamide 10 mg
8. Glibenclamide without problems, previous problems with metformin, did not take yesterday → same as #7
9. Glibenclamide with hypoglycemia symptoms, no previous problems with metformin, took yesterday
   a. Glibenclamide 2.5 mg → metformin 1700 mg
   b. Glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
   c. Glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg
10. Glibenclamide with hypoglycemia or hypoglycemia symptoms, no previous problems with metformin, did not take yesterday → same as #9
11. Glibenclamide with hypoglycemia symptoms, previous problems with metformin, took yesterday
    a. Agrees to take metformin
       i. Glibenclamide 2.5 mg → metformin 850 mg
       ii. Glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
       iii. Glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
    b. Refuses to take metformin
       i. Glibenclamide 2.5 mg → MD consult
       ii. Glibenclamide 5 mg → glibenclamide 2.5 mg
       iii. Glibenclamide 10 mg → glibenclamide 5 mg
12. Glibenclamide with hypoglycemia symptoms, previous problems with metformin, did not take yesterday → same as #11
13. Metformin and glibenclamide without problems, adherent, took glibenclamide yesterday
    a. Metformin 850 mg + glibenclamide any dose → metformin 1700 mg + glibenclamide current dose
    b. Metformin 1700 mg + glibenclamide any dose → metformin 2550 mg + glibenclamide current dose
    c. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 2550 mg + glibenclamide 5 mg
    d. Metformin 2550 mg + glibenclamide 5-10 mg → metformin 2550 mg + glibenclamide 10 mg
14. Metformin and glibenclamide without problems, nonadherent, took glibenclamide yesterday → continue current doses
15. Metformin and glibenclamide without problems, adherent, did not take glibenclamide yesterday → continue current doses
16. Metformin and glibenclamide without problems, nonadherent, did not take glibenclamide yesterday → continue current doses
17. Metformin and glibenclamide, problems with metformin, adherent, took glibenclamide yesterday
    a. Agrees to take metformin
       i. Metformin 850 mg + glibenclamide 2.5 mg → metformin 850 mg + glibenclamide 5 mg
       ii. Metformin 850 mg + glibenclamide 5-10 mg → metformin 850 mg + glibenclamide 10 mg
    b. Refuses to take metformin
       i. Metformin 850 mg + glibenclamide 2.5 mg → glibenclamide 5 mg
       ii. Metformin 850 mg + glibenclamide 5 mg → glibenclamide 10 mg
       iii. Metformin 850 mg + glibenclamide 10 mg → glibenclamide 10 mg, MD consult
    c. Metformin 1700 mg + glibenclamide 2.5 mg → metformin 850 mg + glibenclamide 5 mg
    d. Metformin 1700 mg + glibenclamide 5-10 mg → metformin 850 mg + glibenclamide 10 mg
    e. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 1700 mg + glibenclamide 5 mg

73

      f.   Metformin 2550 mg + glibenclamide 5-10 mg → metformin 1700 mg + glibenclamide 10 mg

18. Metformin and glibenclamide, problems with metformin, nonadherent, took glibenclamide yesterday
    a. Metformin 850 mg + glibenclamide any dose, agrees to take metformin →metformin 850 mg + current glibenclamide dose
    b. Metformin 850 mg + glibenclamide any dose, refuses to take metformin → current glibenclamide dose
    c. Metformin 1700 mg + glibenclamide any dose → metformin 850 mg + current glibenclamide dose
    d. Metformin 2550 mg + glibenclamide any dose → metformin 1700 mg + current glibenclamide dose
19. Metformin and glibenclamide, problems with metformin, adherent, did not take glibenclamide yesterday → same as #18
20. Metformin and glibenclamide, problems with metformin, nonadherent, did not take glibenclamide yesterday → same as #18
21. Metformin and glibenclamide, hypoglycemia symptoms, adherent, took glibenclamide yesterday
    a. Metformin 850 mg + glibenclamide 2.5 mg → metformin 1700 mg
    b. Metformin 850 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
    c. Metformin 850 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg
    d. Metformin 1700 mg + glibenclamide 2.5 mg → metformin 2550 mg
    e. Metformin 1700 mg + glibenclamide 5 mg → metformin 2550 mg + glibenclamide 2.5 mg
    f. Metformin 1700 mg + glibenclamide 10 mg → metformin 2550 mg + glibenclamide 5 mg
    g. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 2550 mg
    h. Metformin 2550 mg + glibenclamide 5 mg → metformin 2550 mg + glibenclamide 2.5 mg
    i. Metformin 2550 mg + glibenclamide 10 mg → metformin 2550 mg + glibenclamide 5 mg
22. Metformin and glibenclamide, hypoglycemia symptoms, nonadherent, took glibenclamide yesterday
    a. Metformin 850 mg + glibenclamide 2.5 mg → metformin 1700 mg
    b. Metformin 850 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
    c. Metformin 850 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg
    d. Metformin 1700 mg + glibenclamide 2.5 mg → metformin 1700 mg
    e. Metformin 1700 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
    f. Metformin 1700 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg
    g. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 2550 mg
    h. Metformin 2550 mg + glibenclamide 5 mg → metformin 2550 mg + glibenclamide 2.5 mg
    i. Metformin 2550 mg + glibenclamide 10 mg → metformin 2550 mg + glibenclamide 5 mg
23. Metformin and glibenclamide, hypoglycemia symptoms, adherent, did not take glibenclamide yesterday → same as #22
24. Metformin and glibenclamide, hypoglycemia symptoms, nonadherent, did not take glibenclamide yesterday → same as #22
25. Metformin and glibenclamide, problems with metformin, hypoglycemia symptoms, adherent, took glibenclamide yesterday
    a. Agrees to take metformin
        i. Metformin 850 mg + glibenclamide 2.5 mg → metformin 850 mg
        ii. Metformin 850 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
        iii. Metformin 850 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
    b. Refuses to take metformin
        i. Metformin 850 mg + glibenclamide 2.5 mg → need MD consult to determine meds
        ii. Metformin 850 mg + glibenclamide 5 mg → glibenclamide 2.5 mg
        iii. Metformin 850 mg + glibenclamide 10 mg → glibenclamide 5 mg

74

      c. Metformin 1700 mg + glibenclamide 2.5 mg → metformin 850 mg
      d. Metformin 1700 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
      e. Metformin 1700 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
      f. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 1700 mg
      g. Metformin 2550 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
      h. Metformin 2550 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg

26. Metformin and glibenclamide, problems with metformin, hypoglycemia symptoms, nonadherent, took glibenclamide yesterday → same as #25
27. Metformin and glibenclamide, problems with metformin, hypoglycemia symptoms, adherent, did not take glibenclamide yesterday → same as #25
28. Metformin and glibenclamide, problems with metformin, hypoglycemia or hypoglycemia symptoms, nonadherent, did not take glibenclamide yesterday → same as #25

400≤FBG<HI
- Urgent MD visit recommended in all cases
  - Patient willing to go
    - Dispense 5 days' worth of meds as a bridge based on 180(200)≤FBG<400 recommendations
    - Arrange appointment
  - Patient unwilling to go
    - Dispense medications based on 180(200)≤FBG<400 recommendations
    - Follow up in 1-3 days

FBG=HI
- Emergent visit recommended in all cases
  - Patient willing to go → arrange emergency transport
  - Patient not willing to go
    - Dispense medications based on 180(200)≤FBG<400 recommendations
    - Follow up in 1 day

PPBG=HI
- Patient is extremely sleepy or confused
  - No
    - Dispense medications based on 180(200)≤FBG<400 recommendations
    - Follow up with FBG in 1-3 days
  - Yes → Emergency visit recommended
    - Patient willing to go → arrange emergency transport
    - Patient not willing to go
      - Dispense medications based on 180(200)≤FBG<400 recommendations
      - Follow up later that day or the next day

Appendix 11 - Month 3 Dosing Recommendations

A1c <5
→Confirm with repeat test. Stop medications, recheck A1c in 3 months

Version #: 1.0

5≤ A1c <6
1. Metformin without problems, adherent
    a. Metformin 850 mg → metformin 850 mg
    b. Metformin 1700 mg → metformin 1700 mg
    c. Metformin 2550 mg → metformin 1700 mg
2. Metformin without problems, nonadherent → stop medications, recheck A1c in 3 months
3. Metformin with problems, adherent
    a. Metformin 850 mg, refuses to take metformin → stop medications, recheck A1c in 3 months
    b. Metformin 850 mg, agrees to take metformin → metformin 850 mg
    c. Metformin 1700 mg → metformin 850 mg
    d. Metformin 2550 mg → metformin 1700 mg
4. Metformin with problems, nonadherent → stop medications, recheck A1c in 3 months
5. Glibenclamide without problems, no previous problems with metformin, adherent
    a. All doses → metformin 1700 mg
6. Glibenclamide without problems, no previous problems with metformin, nonadherent → stop medications, recheck A1c in 3 months
7. Glibenclamide without problems, previous problems with metformin, adherent
    a. All doses, agrees to take metformin → metformin 850 mg
    b. All doses, refuses to take metformin → stop medications, recheck A1c in 3 months
8. Glibenclamide without problems, previous problems with metformin, nonadherent → stop medications, recheck A1c in 3 months
9. Glibenclamide with hypoglycemia or hypoglycemia symptoms, no previous problems with metformin, adherent → same as #5
10. Glibenclamide with hypoglycemia or hypoglycemia symptoms, no previous problems with metformin, nonadherent → stop medications, recheck A1c in 3 months
11. Glibenclamide with hypoglycemia or hypoglycemia symptoms, previous problems with metformin, adherent → same as #7
12. Glibenclamide with hypoglycemia or hypoglycemia symptoms, previous problems with metformin, nonadherent → stop medications, recheck A1c in 3 months
13. Metformin and glibenclamide without problems, adherent
    a. Metformin 850 mg + glibenclamide 2.5-5 mg → metformin 850 mg
    b. Metformin 850 mg + glibenclamide 10 mg → metformin 1700 mg
    c. Metformin 1700-2550 mg + glibenclamide 2.5-5 mg → metformin 1700 mg
    d. Metformin 1700-2550 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 2.5 mg
14. Metformin and glibenclamide without problems, nonadherent
    a. Metformin 850 mg + glibenclamide any dose → metformin 850 mg
    b. Metformin 1700-2550 mg + glibenclamide any dose → metformin 1700 mg
15. Metformin and glibenclamide, problems with metformin, adherent
    a. Agrees to take metformin
        i. Metformin 850 mg + glibenclamide 2.5-5 mg → metformin 850 mg
        ii. Metformin 850 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 2.5 mg
    b. Refuses to take metformin
        i. Metformin 850 mg + glibenclamide 2.5 mg → stop medications, recheck A1c in 3 months
        ii. Metformin 850 mg + glibenclamide 5 mg → glibenclamide 2.5 mg
        iii. Metformin 850 mg + glibenclamide 10 mg → glibenclamide 5 mg
    c. Metformin 1700 mg + glibenclamide 2.5-5 mg → metformin 850 mg

76

       d.   Metformin 1700 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 2.5 mg
       e.   Metformin 2550 mg + glibenclamide 2.5-5 mg → metformin 1700 mg
       f.   Metformin 2550 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 2.5 mg

16. Metformin and glibenclamide, problems with metformin, nonadherent
    a.   Metformin 850 mg + glibenclamide any dose, agrees to take metformin → metformin 850 mg
    b.   Metformin 850 mg + glibenclamide any dose, refuses to take metformin → stop medications, recheck A1c in 3 months
    c.   Metformin 1700 mg + glibenclamide any dose → metformin 850 mg
    d.   Metformin 2550 mg + glibenclamide any dose → metformin 1700 mg

17. Metformin and glibenclamide, hypoglycemia or hypoglycemia symptoms, adherent
    a.   Metformin 850 mg + glibenclamide 2.5-5 mg → metformin 850 mg
    b.   Metformin 850 mg + glibenclamide 10 mg → metformin 1700 mg
    c.   Metformin 1700-2550 mg + glibenclamide any dose → metformin 1700 mg

18. Metformin and glibenclamide, hypoglycemia or hypoglycemia symptoms, nonadherent → same as #14

19. Metformin and glibenclamide, problems with metformin, hypoglycemia or hypoglycemia symptoms, adherent
    a.   Metformin 850 mg + glibenclamide any dose, agrees to take metformin → metformin 850 mg
    b.   Metformin 850 mg + glibenclamide any dose, refuses to take metformin → stop medications, recheck A1c in 3 months
    c.   Metformin 1700 mg + glibenclamide any dose → metformin 850 mg
    d.   Metformin 2550 mg + glibenclamide any dose → metformin 1700 mg

20. Metformin and glibenclamide, problems with metformin, hypoglycemia or hypoglycemia symptoms, nonadherent → same as #16

6≤ A1c ≤Tx goal

1. Metformin without problems, adherent
    a.   Metformin 850 mg → metformin 850 mg
    b.   Metformin 1700 mg → metformin 1700 mg
    c.   Metformin 2550 mg → metformin 2550 mg

2. Metformin without problems, nonadherent
    a.   Metformin 850 mg → metformin 850 mg
    b.   Metformin 1700-2550 mg → metformin 1700 mg

3. Metformin with problems, adherent
    a.   Metformin 850 mg, agrees to take metformin → metformin 850 mg
    b.   Metformin 850 mg, refuses to take metformin → glibenclamide 2.5 mg
    c.   Metformin 1700 mg → metformin 850 mg
    d.   Metformin 2550 mg → metformin 1700 mg

4. Metformin with problems, nonadherent → same as #3

5. Glibenclamide without problems, no previous problems with metformin, adherent
    a.   All doses → metformin 1700 mg

6. Glibenclamide without problems, no previous problems with metformin, nonadherent → same as #5

7. Glibenclamide without problems, previous problems with metformin, adherent
    a.   Willing to take metformin
       i.   Glibenclamide 2.5 mg → metformin 850 mg
       ii.   Glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
       iii.   Glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
    b.   Refuses to take metformin → current dose of glibenclamide

Version #: 1.0

8. Glibenclamide without problems, previous problems with metformin, nonadherent
    a. Willing to take metformin
        i. Glibenclamide 2.5 mg → metformin 850 mg
        ii. Glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
        iii. Glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
    b. Refuses to take metformin
        i. Glibenclamide 2.5 mg → stop medications, recheck A1c in last 3 months
        ii. Glibenclamide 5 mg → glibenclamide 2.5 mg
        iii. Glibenclamide 10 mg → glibenclamide 5 mg
9. Glibenclamide with hypoglycemia or hypoglycemia symptoms, no previous problems with metformin, adherent → same as #5
10. Glibenclamide with hypoglycemia or hypoglycemia symptoms, no previous problems with metformin, nonadherent → same as #5
11. Glibenclamide with hypoglycemia or hypoglycemia symptoms, previous problems with metformin, adherent
    a. Agrees to take metformin
        i. Glibenclamide 2.5-5 mg → metformin 850 mg
        ii. Glibenclamide 10 mg → metformin 850 mg + glibenclamide 2.5 mg
    b. Refuses to take metformin
        i. Glibenclamide 2.5 mg → stop medications, recheck A1c in 3 months
        ii. Glibenclamide 5 mg → glibenclamide 2.5 mg
        iii. Glibenclamide 10 mg → glibenclamide 5 mg
12. Glibenclamide with hypoglycemia or hypoglycemia symptoms, previous problems with metformin, nonadherent → same as #11
13. Metformin and glibenclamide without problems, adherent → continue current doses
14. Metformin and glibenclamide without problems, nonadherent
    a. Metformin any dose + glibenclamide 2.5 mg → metformin current dose
    b. Metformin any dose + glibenclamide 5 mg → metformin current dose + glibenclamide 2.5 mg
    c. Metformin any dose + glibenclamide 10 mg → metformin current dose + glibenclamide 5 mg
15. Metformin and glibenclamide, problems with metformin, adherent
    a. Metformin 850 mg + glibenclamide any dose, agrees to take metformin →metformin 850 mg + current glibenclamide dose
    b. Metformin 850 mg + glibenclamide any dose, refuses to take metformin → current glibenclamide dose
    c. Metformin 1700 mg + glibenclamide any dose → metformin 850 mg + current glibenclamide dose
    d. Metformin 2550 mg + glibenclamide any dose → metformin 1700 mg + current glibenclamide dose
16. Metformin and glibenclamide, problems with metformin, nonadherent
    a. Agrees to take metformin
        i. Metformin 850 mg + glibenclamide 2.5 mg → metformin 850 mg
        ii. Metformin 850 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
        iii. Metformin 850 mg + glibenclamide 10 mg → metformin 850 mg+ glibenclamide 5 mg
    b. Refuses to take metformin
        i. Metformin 850 mg + glibenclamide 2.5 mg → stop medications, recheck A1c in 3 months
        ii. Metformin 850 mg + glibenclamide 5 mg → glibenclamide 2.5 mg
        iii. Metformin 850 mg + glibenclamide 10 mg → glibenclamide 5 mg
    c. Metformin 1700 mg + glibenclamide 2.5 mg → metformin 850 mg

78

    d. Metformin 1700 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
    e. Metformin 1700 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
    f. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 1700 mg
    g. Metformin 2550 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
    h. Metformin 2550 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg

17. Metformin and glibenclamide, hypoglycemia or hypoglycemia symptoms, adherent
    a. Metformin any dose + glibenclamide 2.5 mg → metformin current dose
    b. Metformin any dose + glibenclamide 5 mg → metformin current dose + glibenclamide 2.5 mg
    c. Metformin any dose + glibenclamide 10 mg → metformin current dose + glibenclamide 5 mg

18. Metformin and glibenclamide, hypoglycemia or hypoglycemia symptoms, nonadherent → same as #17

19. Metformin and glibenclamide, problems with metformin, hypoglycemia or hypoglycemia symptoms, adherent
    a. Agrees to take metformin
        i. Metformin 850 mg + glibenclamide 2.5 mg → metformin 850 mg
        ii. Metformin 850 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
        iii. Metformin 850 mg + glibenclamide 10 mg → metformin 850 mg+ glibenclamide 5 mg
    b. Refuses to take metformin
        i. Metformin 850 mg + glibenclamide 2.5 mg → stop medications, recheck A1c in 3 months
        ii. Metformin 850 mg + glibenclamide 5 mg → glibenclamide 2.5 mg
        iii. Metformin 850 mg + glibenclamide 10 mg → glibenclamide 5 mg
    c. Metformin 1700 mg + glibenclamide 2.5 mg → metformin 850 mg
    d. Metformin 1700 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
    e. Metformin 1700 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
    f. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 1700 mg
    g. Metformin 2550 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
    h. Metformin 2550 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg

20. Metformin and glibenclamide, problems with metformin, hypoglycemia or hypoglycemia symptoms, nonadherent → same as #19

Tx goal< A1c <9 AND FBG >130(150) OR PPBG >180(200
1. Metformin without problems, adherent
    a. Metformin 850 mg → metformin 1700 mg
    b. Metformin 1700 mg → metformin 2550 mg
    c. Metformin 2550 mg → metformin 2550 mg + glibenclamide 2.5 mg
2. Metformin without problems, nonadherent
    a. Metformin 850 mg → metformin 1700 mg
    b. Metformin 1700 mg → metformin 1700 mg
    c. Metformin 2550 mg → metformin 2550 mg
3. Metformin with problems, adherent
    a. Metformin 850 mg, agrees to take metformin → metformin 850 mg + glibenclamide 2.5 mg
    b. Metformin 850 mg, refuses to take metformin → glibenclamide 2.5 mg
    c. Metformin 1700 mg → metformin 850 mg + glibenclamide 2.5 mg
    d. Metformin 2550 mg → metformin 1700 mg + glibenclamide 2.5 mg
4. Metformin with problems, nonadherent → same as #3
5. Glibenclamide without problems, no previous problems with metformin, adherent
    a. Any dose → metformin 1700 mg + glibenclamide current dose
6. Glibenclamide without problems, no previous problems with metformin, nonadherent

79

        a. All doses → metformin 1700 mg
7. Glibenclamide without problems, previous problems with metformin, adherent
    a. Glibenclamide any dose, agrees to take metformin → metformin 850 mg + current glibenclamide dose
    b. Refuses to take metformin
        i. Glibenclamide 2.5 mg → glibenclamide 5 mg
        ii. Glibenclamide 5 mg → glibenclamide 10 mg
        iii. Glibenclamide 10 mg → glibenclamide 10 mg
8. Glibenclamide without problems, previous problems with metformin, nonadherent
    a. Willing to take metformin
        i. Glibenclamide 2.5 mg → metformin 850 mg
        ii. Glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
        iii. Glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
    b. Refuses to take metformin → continue current glibenclamide dose
9. Glibenclamide with hypoglycemia or hypoglycemia symptoms, no previous problems with metformin, adherent
    a. Glibenclamide 2.5-5 mg → metformin 1700 mg
    b. Glibenclamide 10 mg → metformin 1700 mg + glibenclamide 2.5 mg
10. Glibenclamide with hypoglycemia or hypoglycemia symptoms, no previous problems with metformin, nonadherent → same as #9
11. Glibenclamide with hypoglycemia or hypoglycemia symptoms, previous problems with metformin, adherent
    a. Agrees to take metformin
        i. Glibenclamide 2.5 mg → metformin 850 mg
        ii. Glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
        iii. Glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
    b. Refuses to take metformin
        i. Glibenclamide 2.5 mg → MD consult
        ii. Glibenclamide 5 mg → glibenclamide 2.5 mg
        iii. Glibenclamide 10 mg → glibenclamide 5 mg
12. Glibenclamide with hypoglycemia or hypoglycemia symptoms, previous problems with metformin, nonadherent → same as #11
13. Metformin and glibenclamide without problems, adherent
    a. Metformin 850 mg + glibenclamide any dose → metformin 1700 mg + current glibenclamide dose
    b. Metformin 1700 mg + glibenclamide any dose → metformin 2550 mg + glibenclamide current dose
    c. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 2550 mg + glibenclamide 5 mg
    d. Metformin 2550 mg + glibenclamide 5 mg → metformin 2550 mg + glibenclamide 10 mg
    e. Metformin 2550 mg + glibenclamide 10 mg → metformin 2550 mg + glibenclamide 10 mg
14. Metformin and glibenclamide without problems, nonadherent → continue current doses
15. Metformin and glibenclamide, problems with metformin, adherent
    a. Agrees to take metformin
        i. Metformin 850 mg + glibenclamide 2.5 mg → metformin 850 mg + glibenclamide 5 mg
        ii. Metformin 850 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 10 mg
        iii. Metformin 850 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 10 mg
    b. Refuses to take metformin
        i. Metformin 850 mg + glibenclamide 2.5 mg → glibenclamide 5 mg

       ii.   Metformin 850 mg + glibenclamide 5 mg → glibenclamide 10 mg

       iii.   Metformin 850 mg + glibenclamide 10 mg → glibenclamide 10 mg

  c. Metformin 1700 mg + glibenclamide 2.5 mg → metformin 850 mg + glibenclamide 5 mg

  d. Metformin 1700 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 10 mg

  e. Metformin 1700 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 10 mg

  f. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 1700 mg + glibenclamide 5 mg

  g. Metformin 2550 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 10 mg

  h. Metformin 2550 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 10 mg

16. Metformin and glibenclamide, problems with metformin, nonadherent
    a. Metformin 850 mg + glibenclamide any dose, agrees to take metformin → metformin 850 mg + current glibenclamide dose
    b. Metformin 850 mg + glibenclamide any dose, refuses to take metformin → current glibenclamide dose
    c. Metformin 1700 mg + glibenclamide any dose → metformin 850 mg + current glibenclamide dose
    d. Metformin 2550 mg + glibenclamide any dose → metformin 1700 mg + current glibenclamide dose

17. Metformin and glibenclamide, hypoglycemia or hypoglycemia symptoms, adherent
    a. Metformin 850 mg + glibenclamide 2.5 mg → metformin 1700 mg
    b. Metformin 850 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
    c. Metformin 850 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg
    d. Metformin 1700 mg + glibenclamide 2.5 mg → metformin 2550 mg
    e. Metformin 1700 mg + glibenclamide 5 mg → metformin 2550 mg + glibenclamide 2.5 mg
    f. Metformin 1700 mg + glibenclamide 10 mg → metformin 2550 mg + glibenclamide 5 mg
    g. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 2550 mg
    h. Metformin 2550 mg + glibenclamide 5 mg → metformin 2550 mg + glibenclamide 2.5 mg
    i. Metformin 2550 mg + glibenclamide 10 mg → metformin 2550 mg + glibenclamide 5 mg

18. Metformin and glibenclamide, hypoglycemia or hypoglycemia symptoms, nonadherent → same as #17

19. Metformin and glibenclamide, problems with metformin, hypoglycemia or hypoglycemia symptoms, adherent
    a. Agrees to take metformin
       i. Metformin 850 mg + glibenclamide 2.5 mg → metformin 850 mg
       ii. Metformin 850 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
       iii. Metformin 850 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
    b. Refuses to take metformin
       i. Metformin 850 mg + glibenclamide 2.5 mg → MD consult
       ii. Metformin 850 mg + glibenclamide 5 mg → glibenclamide 2.5 mg
       iii. Metformin 850 mg + glibenclamide 10 mg → glibenclamide 5 mg
    c. Metformin 1700 mg + glibenclamide 2.5 mg → metformin 850 mg
    d. Metformin 1700 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
    e. Metformin 1700 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
    f. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 1700 mg
    g. Metformin 2550 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
    h. Metformin 2550 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg

20. Metformin and glibenclamide, problems with metformin, hypoglycemia or hypoglycemia symptoms, nonadherent → same as #19

Tx goal< A1c <9 AND [FBG ≤130(150) OR PPBG ≤180(200)] → Use dosing recommendations for 6≤ A1c ≤Tx goal

9≤ A1c ≤14 AND FBG >130(150) OR PPBG >180(200)
1. Metformin without problems, adherent
    a. Metformin 850 mg → metformin 1700 mg + glibenclamide 2.5 mg
    b. Metformin 1700 mg → metformin 1700 mg + glibenclamide 2.5 mg
    c. Metformin 2550 mg → metformin 2550 mg + glibenclamide 2.5 mg
2. Metformin without problems, nonadherent
    a. Metformin 850 mg → metformin 1700 mg
    b. Metformin 1700 mg → metformin 1700 mg
    c. Metformin 2550 mg → metformin 2550 mg
3. Metformin with problems, adherent
    a. Metformin 850 mg, agrees to take metformin → metformin 850 mg + glibenclamide 2.5 mg
    b. Metformin 850 mg, refuses to take metformin → glibenclamide 2.5 mg
    c. Metformin 1700 mg → metformin 850 mg + glibenclamide 2.5 mg
    d. Metformin 2550 mg → metformin 1700 mg + glibenclamide 2.5 mg
4. Metformin with problems, nonadherent → same as #3
5. Glibenclamide without problems, no previous problems with metformin, adherent
    a. All doses → metformin 1700 mg +glibenclamide current dose
6. Glibenclamide without problems, no previous problems with metformin, nonadherent
    a. All doses → metformin 1700 mg + glibenclamide 2.5 mg
7. Glibenclamide without problems, previous problems with metformin, adherent
    a. Agrees to take metformin → metformin 850 mg + glibenclamide current dose
    b. Refuses to take metformin
        i. Glibenclamide 2.5 mg → glibenclamide 5 mg
        ii. Glibenclamide 5 mg → glibenclamide 10 mg
        iii. Glibenclamide 10 mg → glibenclamide 10 mg
8. Glibenclamide without problems, previous problems with metformin, nonadherent
    a. Agrees to take metformin
        i. Glibenclamide 2.5-5 mg → metformin 850 mg + glibenclamide 2.5 mg
        ii. Glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
    b. Refuses to take metformin → continue current glibenclamide dose
9. Glibenclamide with hypoglycemia or hypoglycemia symptoms, no previous problems with metformin, adherent
    a. Glibenclamide 2.5 mg → metformin 1700 mg
    b. Glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
    c. Glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg
10. Glibenclamide with hypoglycemia or hypoglycemia symptoms, no previous problems with metformin, nonadherent → same as #9
11. Glibenclamide with hypoglycemia or hypoglycemia symptoms, previous problems with metformin, adherent
    a. Agrees to take metformin
        i. Glibenclamide 2.5 mg → metformin 850 mg
        ii. Glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
        iii. Glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
    b. Refuses to take metformin

82

Version #: 1.0

        i.   Glibenclamide 2.5 mg → MD consult
       ii.   Glibenclamide 5 mg → glibenclamide 2.5 mg
      iii.   Glibenclamide 10 mg → glibenclamide 5 mg

12. Glibenclamide with hypoglycemia or hypoglycemia symptoms, previous problems with metformin, nonadherent → same as #11
13. Metformin and glibenclamide without problems, adherent
   a. Metformin 850 mg + glibenclamide any dose → metformin 1700 mg + current glibenclamide dose
   b. Metformin 1700 mg + glibenclamide any dose → metformin 2550 mg + glibenclamide current dose
   c. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 2550 mg + glibenclamide 5 mg
   d. Metformin 2550 mg + glibenclamide 5 mg → metformin 2550 mg + glibenclamide 10 mg
   e. Metformin 2550 mg + glibenclamide 10 mg → metformin 2550 mg + glibenclamide 10 mg
14. Metformin and glibenclamide without problems, nonadherent → continue current doses
15. Metformin and glibenclamide, problems with metformin, adherent
   a. Agrees to take metformin
      i. Metformin 850 mg + glibenclamide 2.5 mg → metformin 850 mg + glibenclamide 5 mg
      ii. Metformin 850 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 10 mg
      iii. Metformin 850 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 10 mg
   b. Refuses to take metformin
      i. Metformin 850 mg + glibenclamide 2.5 mg → glibenclamide 5 mg
      ii. Metformin 850 mg + glibenclamide 5 mg → glibenclamide 10 mg
      iii. Metformin 850 mg + glibenclamide 10 mg → glibenclamide 10, mg
   c. Metformin 1700 mg + glibenclamide 2.5 mg → metformin 850 mg + glibenclamide 5 mg
   d. Metformin 1700 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 10 mg
   e. Metformin 1700 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 10
   f. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 1700 mg + glibenclamide 5 mg
   g. Metformin 2550 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 10 mg
   h. Metformin 2550 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 10 mg
16. Metformin and glibenclamide, problems with metformin, nonadherent
   a. Metformin 850 mg + glibenclamide any dose, agrees to take metformin → metformin 850 mg + current glibenclamide dose
   b. Metformin 850 mg + glibenclamide any dose, refuses to take metformin → current glibenclamide dose
   c. Metformin 1700 mg + glibenclamide any dose → metformin 850 mg + current glibenclamide dose
   d. Metformin 2550 mg + glibenclamide any dose → metformin 1700 mg + current glibenclamide dose
17. Metformin and glibenclamide, hypoglycemia or hypoglycemia symptoms, adherent
   a. Metformin 850 mg + glibenclamide 2.5 mg → metformin 1700 mg
   b. Metformin 850 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
   c. Metformin 850 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg
   d. Metformin 1700 mg + glibenclamide 2.5 mg → metformin 2550 mg
   e. Metformin 1700 mg + glibenclamide 5 mg → metformin 2550 mg + glibenclamide 2.5 mg
   f. Metformin 1700 mg + glibenclamide 10 mg → metformin 2550 mg + glibenclamide 5 mg
   g. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 2550 mg
   h. Metformin 2550 mg + glibenclamide 5 mg → metformin 2550 mg + glibenclamide 2.5 mg
   i. Metformin 2550 mg + glibenclamide 10 mg → metformin 2550 mg + glibenclamide 5 mg
18. Metformin and glibenclamide, hypoglycemia or hypoglycemia symptoms, nonadherent → same as #17

83

19. Metformin and glibenclamide, problems with metformin, hypoglycemia or hypoglycemia symptoms, adherent
    a. Agrees to take metformin
        i. Metformin 850 mg + glibenclamide 2.5 mg → metformin 850 mg
        ii. Metformin 850 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
        iii. Metformin 850 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
    b. Refuses to take metformin
        i. Metformin 850 mg + glibenclamide 2.5 mg → MD consult
        ii. Metformin 850 mg + glibenclamide 5 mg → glibenclamide 2.5 mg
        iii. Metformin 850 mg + glibenclamide 10 mg → glibenclamide 5 mg
    c. Metformin 1700 mg + glibenclamide 2.5 mg → metformin 850 mg
    d. Metformin 1700 mg + glibenclamide 5 mg → metformin 850 mg + glibenclamide 2.5 mg
    e. Metformin 1700 mg + glibenclamide 10 mg → metformin 850 mg + glibenclamide 5 mg
    f. Metformin 2550 mg + glibenclamide 2.5 mg → metformin 1700 mg
    g. Metformin 2550 mg + glibenclamide 5 mg → metformin 1700 mg + glibenclamide 2.5 mg
    h. Metformin 2550 mg + glibenclamide 10 mg → metformin 1700 mg + glibenclamide 5 mg
20. Metformin and glibenclamide, problems with metformin, hypoglycemia or hypoglycemia symptoms, nonadherent → same as #19

9≤ A1c ≤14 AND [FBG ≤130(150) OR PPBG ≤180(200)] → Use dosing recommendations for Tx goal< A1c <9

A1c >14
- Coordinator/MD consult for all cases

Appendix 12 - Blood Pressure Protocol

Version #: 1.0

```
                    ┌──────────────────────────────────────────┐
                    │ CHW checks blood pressure with automatic cuff │
                    └──────────────────────────────────────────┘
```

CHW checks blood pressure with automatic cuff

SBP[1] 90-140[2] and DBP[3] <90

SBP <90

SBP ≥140 OR DBP ≥90

Repeat BP measurement

Continue with visit

SBP 90-140 and DBP <90

SBP <90

SBP 140-160 and DBP <100

SBP 160-200 and DBP <120

SBP ≥200 OR DBP ≥120

Continue with visit

Low BP confirmed (taken into account for patients with possible infected ulcers). Continue with visit

Continue with visit, non-urgent referral

Continue with visit, urgent referral

Emergency referral

1. SBP = systolic blood pressure
2. All blood pressure in mmHg
3. DBP = diastolic blood pressure

85