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Research Paper

Effect of a structured pharmacist-led medication therapy management intervention on glycemic control and medication adherence in adults with type 2 diabetes mellitus: a randomized controlled trial protocol

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ABSTRACT

Background: 537 million adults are suffering from Type 2 diabetes mellitus (T2DM) globally. Poor medication adherence is one of the largest factors that can be modified in achieving glycemic control. Although randomized evidence-based studies of structured pharmacist-led medication therapy management (MTM) are limited, community pharmacists are well suited to deliver structured MTM.

Objective: The goal was to assess the effect of a structured MTM intervention provided by a pharmacist on glycated hemoglobin (HbA1c) and medication adherence at 6 months compared with usual pharmacist care in adults with T2DM.

Methods: This parallel group, two-arm randomized controlled trial (RCT) will include adults age ≥18 years with type 2 diabetes (T2DM) confirmed, HbA1c ≥7.5%, and at least one oral antihyperglycemic and/or one injectable non-insulin agent as prescribed. Participants will be assigned to either a six-month, 5 contact pharmacist-led MTM group or a group receiving usual pharmacy care at random. Participants will be randomized between pharmacist-led MTM (5 contacts / 6 months) and usual pharmacy care. The key outcome is change in HbA1c between the groups at six months. Secondary outcomes are MMAS-8 score, blood pressure, LDL cholesterol, medication possession ratio and acute care utilization for diabetes. Sustainability will be evaluated in a 12 month follow-up. There are 20% attrition, so 80% of 270 participants will be present to provide 80% power. Data will be analysed based on intention to treat principle, with mixed effects models.

Results: As this is a protocol, no outcome data are currently available. Planned analyses will include assessment of intervention effects and sustainability.

Conclusion: This study is sufficiently powered to evaluate the effectiveness of structured pharmacist-led MTM on glycemic control and adherence to drugs in adults with T2DM.

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1. INTRODUCTION

1.1 Background and Rationale

Type 2 diabetes mellitus (T2DM), which represents about 90% of the estimated 783 million diabetes cases worldwide in 2045, is a common type of diabetes [1]. Costs are high: diabetes-related health expenditure was over 1.3 trillion US dollars in 2015 and will reach over 2.1 trillion by 2030, due to increased prevalence and treatment [2]. The UK Prospective Diabetes Study (UKPDS 1–10) showed that sustained glycemic control decreases the risk of microvascular and, after a longer period of follow-up, macrovascular complications, particularly for intensive glucose management with insulin or sulfonylureas compared with conventional treatment [3]. Regardless of this evidence, it is recognized that many patients with T2DM fail to meet guideline HbA1c targets and medication adherence is one of the biggest modifiable factors responsible for this.

Community pharmacists are the most commonly visited and geographically widespread health care professionals in many health care systems, and are in a good position to provide structured, longitudinal medication therapy management (MTM) [4]. This new clinical role has evolved from the initial definition of pharmaceutical care as the responsible delivery of drug therapy to achieve benefits for a patient's quality of life, which includes medication reconciliation, adherence counselling, identification and resolution of drug related problems, and structured prescriber communication [5]. Non-adherence is not uncommon and is not exclusive to chronic conditions: a large minority to majority of those with chronic conditions is estimated not to take medications as prescribed, influenced by condition-related, therapy-related, socio-economic, health-system, and patient-related factors [6]. The downstream cost is significant, and morbidity, hospitalization, mortality costs due to non-adherence are estimated to be tens of billions of dollars per year, as a result of not adhering to a treatment regimen. [7] Nonadherence to antihyperglycemic agents is directly associated with poor glycemic control, increased risk of complications, and increased use of healthcare resources in the realm of T2DM, making it an obvious pharmacist-intervention target.

Frequent contact with patients on chronic pharmacotherapy has occurred from community pharmacies, but the establishment of a standardized, rigorous, repeatable intervention with demonstrated glycemic and adherence impact has been challenging due to the variability of published interventions in content, duration, and outcome measures. This protocol is designed to fill that void by defining, prior to enrollment, an RCT of a standard 5-contact MTM intervention using a pre-specified dual glycemic/adherence outcome structure to provide replicable evidence for use in community pharmacy practice.

1.2 Objectives

Primary Aim: To assess the clinical and statistical significance of the HbA1c reduction at 6-months post structured, pharmacist-led MTM intervention compared with usual pharmacy care in adults with T2DM.

Secondary Objectives: To establish the effect of interventions on (i) medication adherence (8-item Morisky Medication Adherence Scale, MMAS-8); (ii) blood pressure and LDL; (iii) refill-based medication possession ratio; (iv) diabetes-related emergency department visits or hospitalizations; and (v) maintenance of intervention benefits at 12 months after the final intervention contact.

1.3 Trial Hypotheses

H1: The pharmacist-led MTM group will achieve significantly larger reductions in HbA1c compared with usual-care at 6 months.

H2: MMAS-8 scores will be significantly higher in the intervention group at 6 months compared to the control group.

H3: HbA1c and MMAS-8 will show between group differences that will diminish but still be clinically measurable at the sustainability follow-up at 12 months.

2. RELATED WORK

2.1 Pharmacist-Led Interventions in Type 2 Diabetes

There has been an increasing number of systematic and umbrella reviews that have assessed the effectiveness of pharmacist-led interventions with regard to outcomes associated with chronic disease. A pharmacist-led intervention in primary care for T2DM resulted in a statistically significant reduction in HbA1c (−0.67; 95% CI −0.87 to −0.48) compared to usual care with greater effects when delivered monthly and when baseline HbA1c was >8.5% [8]. A community-based review of pharmacist-led chronic disease management also demonstrated substantial decreases in HbA1c, total cholesterol, LDL cholesterol, and blood pressure, and improved adherence, in diabetes, hypertension, dyslipidemia, heart failure and respiratory disease [4]. The same review highlighted that economic and utilization results were still rather limited and focused on diabetes studies, with a lack of evidence on downstream effects, such as acute care utilization.

Individual trials confirm this continuum and demonstrate the variation in the intervention design that is found across different settings and contexts for translation. One study conducted in a two-arm, parallel, single-blind randomized control trial (RCT) of hypertension education using structured counselling in multiple visits to pharmacists showed clinically significant blood pressure reductions compared with usual care [9]. Although this is a trial in a different disease domain, it demonstrates the feasibility of structured, multi-contact pharmacist interventions within the natural context of the pharmacy workflow, and the necessity of a carefully designed, easily replicable protocol, which is missing from many previous trials in which pharmacists led interventions in diabetes, and present in this protocol, with a structured 5-contact schedule and an explicit, standardized session checklist.

2.2 Medication Adherence as an Intervention Target

In addition to the glycemic literature, research on adherence to treatment has also been the foundation for a direct focus on adherence, rather than treating it merely as a mediator of glycemic outcomes. Non-adherence is best viewed not as a patient characteristic, but as a dynamic interplay between the patient's motivation and ability in the disease and treatment environment or context [6]. The review of the systematic reviews of the clinical and economic consequences of non-adherence to medication for various chronic conditions concluded that interventions that incorporate a clinical and adherence counselling component, like structured MTM, were consistently related to poorer clinical outcomes and significant higher costs than interventions that focused on adherence counselling or clinical review alone [10]. The cost of non-adherence-related morbidity and mortality is estimated to be tens of billions of dollars per year in the United States [7] and thus the importance of adherence and clinical outcome-related interventions at the system and individual level.

2.3 Behavioral and Digital Adjuncts to Pharmacist Counselling

The adherence-counselling component of this protocol includes motivational-interingering techniques which have been shown to have a solid evidence base in T2DM. META analysis of RCTs that assessed TI-based MI in adults with T2DM showed a significant pooled reduction in HbA1c among interventionists compared to placebo, as well as self-management and self-efficacy improvements among interventionists [11]. Digital adjuncts and mobile-health have been investigated individually to provide adherence support (between contacts) and one feasibility trial of a smartphone medication-reminder app

in a multiethnic Asian T2DM population demonstrated acceptable engagement as well as a potential benefit for adherence, which were not powered for glycemic endpoints [12]. The findings highlighted the need to anchor the present intervention to pharmacist delivered motivational-interviewing counselling, and then consider digital tools as potentially supportive rather than a replacement to counselling, due to less mature evidence base for digital interventions in this population.

2.4 Economic and Health-System Considerations

An additional literature stream relates to the economic arguments for pharmacist-led chronic disease services. Pharmacist-led diabetes interventions have been shown to repeatedly improve intermediate clinical markers associated with decreased risk of long-term complications [4], [8] and a structured MTM service has the potential to offset its delivery cost through reduced downstream utilization, especially considering the fact that non-adherence-related morbidity and mortality represents tens of billions of dollars in avoidable health care expenditure annually [7]. As discussed in Section 2.1, there is, however, a relatively limited number of direct evidence on utilization and cost outcomes of pharmacist-led diabetes interventions [4]. The secondary outcomes of the study will include diabetes-related visit to the ED and hospitalisation, which will provide evidence on the use of services as part of the trial, and will be included in this protocol as an additional strand of evidence relevant to utilisation.The secondary outcomes of this study will be diabetes-related visits to the ED and hospitalisations, which will provide evidence on the use of services as an additional strand of evidence to this protocol, but the trial is not powered as a formal economic evaluation.

2.5 Gap Addressed by This Protocol

The literature provides evidence that collectively suggests a possible clinically significant MTM effect on glycemic control and a separate MTM effect on adherence; however, there are three gaps in the literature that this protocol fills. Few trials are prespecified to have a glycemic/adherence outcome structure in a single, adequately powered trial, thereby precluding mechanistic interpretation of any glycemic effect. Second, in the current literature, different interventions are documented, and each of these has a different intervention content, contact schedule, and fidelity-monitoring procedures. This trial therefore explicitly specifies the intervention content, contact schedule, and fidelity-monitoring procedures, in advance, consistent with SPIRIT [8] to ensure that the pooled effect estimate applies to a standardized protocol for a new trial. Third, very few trials include a sustainability follow-up long enough to differentiate a lasting effect from one that is limited to the active period, which is what is done here through an explicit 12-month assessment, three months post-final contact.

3. METHODOLOGY

3.1 Trial Design

It is a 2 arm parallel group superiority randomized controlled trial (RCT) with a ratio of 1:1 allocation of community pharmacy sites, and where feasible, outcome measurements will be blinded to allocation, but participant/pharmacist blinding will not be possible due to the nature of the behavioral intervention. The trial is registered using the SPIRIT 2013 checklist [13], [14] and completed trial will be reported as per CONSORT 2010 [15].

3.2 Study Setting

The trial will be of community pharmacies that have a minimum set of required features (private consultation room, electronic dispensing record, and at least one pharmacist with study MTM protocol training). A site-selection appendix will be developed and reported before enrollment that will include site eligibility, training, and fidelity-monitoring procedures. Delivering pharmacists will undergo standardized training on the medication-reconciliation checklist, motivational-interviewing techniques similar to other T2DM trials [11] and structured goal setting, and then a competency check-off prior to the start of

participant enrolment. The aim of this training is to limit inter-pharmacist variability, which is a limitation of the heterogeneous prior literature (Section 2.1), and to aid in the fidelity auditing of Section 3.11.

3.3 Eligibility Criteria

Participants are eligible to be entered in the study if they have been diagnosed with T2DM and have suboptimal glycaemic control to enable meaningful involvement in structured counselling and have not been excluded for not being able to interpret results (e.g., as a result of type 1 or secondary diabetes diagnosis) or for 12-month retention. Inclusion criteria are that the initial screening HbA1c must be ≥7.5% (providing room for measurable improvement) and that prescription history for the prior three months is required from a participating pharmacy to assess adherence via refills (See Table 1).

Table 1. Participant Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
Age 18 years or older	Type 1 diabetes mellitus or secondary/gestational diabetes
Confirmed T2DM diagnosis (physician-documented or per ADA diagnostic criteria)	HbA1c below 7.5% at screening (insufficient room for improvement)
HbA1c 7.5% or higher at screening	Current enrollment in another structured diabetes self-management or MTM program
Currently prescribed one or more oral antihyperglycemic or non-insulin injectable agent	Cognitive impairment precluding informed consent or participation in counselling sessions
Able to provide written informed consent	Planned relocation or pharmacy transfer within the 12-month follow-up period
Filling prescriptions at a participating pharmacy for 3 months or more prior to enrollment	Terminal illness with life expectancy under 12 months
—	Current participation in another interventional clinical trial

3.4 Interventions

Intervention Arm (pharmacist-led MTM): MTM will include 5 structured, individual, 20-30 minute contacts by the pharmacist at baseline, 1, 2, 3, and 6 months, focused on: (i) comprehensive medication reconciliation and identification of drug-related problems, in keeping with the framework of pharmaceutical-care in which the pharmacist takes responsibility for drug-therapy outcomes [5]; (ii) structured adherence counselling using the techniques of motivational-interviewing as shown to be effective in improving glycemic and self-management outcomes in T2DM [11]; (iii) individualized goal-setting for glycemic and lifestyle goals; (iv) a written treatment plan shared with the participant and also, with the participant's consent, the prescribing physician; and (v) structured escalation of drug-related problems (dosing, therapeutic duplication, adverse effects etc.) to the prescriber through a standardized form. A brief telephone contact at month-2 instead of in-person visit to reduce burden. Intervention fidelity will be monitored using a standardized checklist with a random 10% of sessions being audited.

Control Arm (Usual Care): These participants will receive standard pharmacy dispensing, counselling that is typically provided at the time of dispensing, and will not be prohibited from accessing other routine care, but they will not have access to the structured MTM protocol, goal-setting or prescriber-communication element. As expected in a pragmatic design, both arms continue to receive the care they receive from their usual treating doctors and there is no restriction on pharmacotherapy.

3.5 Outcomes

The main analysis will be the difference in change in lab measured HbA1c between the groups at 6 months. Secondary and safety outcomes, detailed in Table 2, include measures of adherence, as well as measures of the cardio metabolic and utilization and safety domains at multiple time points, enabling the dual glycemic/adherence hypothesis structure (Section 1.3) to be tested in a single trial.

Table 2. Primary and Secondary Outcome Measures

Outcome	Measure/Instrument	Time Point(s)
Primary: Glycemic control	HbA1c (%), laboratory-measured	Baseline, 6 months
Secondary: Medication adherence	8-item Morisky Medication Adherence Scale (MMAS-8) [16]	Baseline, 3, 6, 12 months
Secondary: Blood pressure	Systolic/diastolic blood pressure (mmHg), standardized measurement	Baseline, 6, 12 months
Secondary: Lipid profile	LDL cholesterol (mmol/L)	Baseline, 6, 12 months
Secondary: Refill-based adherence	Medication possession ratio (proportion of days covered), pharmacy dispensing records	Continuous, summarized at 6, 12 months
Secondary: Acute care utilization	Diabetes-related emergency department visits and hospitalizations (self-report, verified against records where accessible)	6, 12 months
Sustainability: Glycemic control and adherence	HbA1c and MMAS-8	12 months (6 months after final intervention contact)
Safety: Adverse events	Hypoglycemic episodes and other adverse events, structured questioning at each contact	Every study contact

3.6 Participant Timeline

The enrolment and intervention schedule for the SPIRIT program is shown in Figure 1, with outcome assessments superimposed in the figure, corresponding to the intervention contacts and two follow-up windows outlined in Section 3.5.

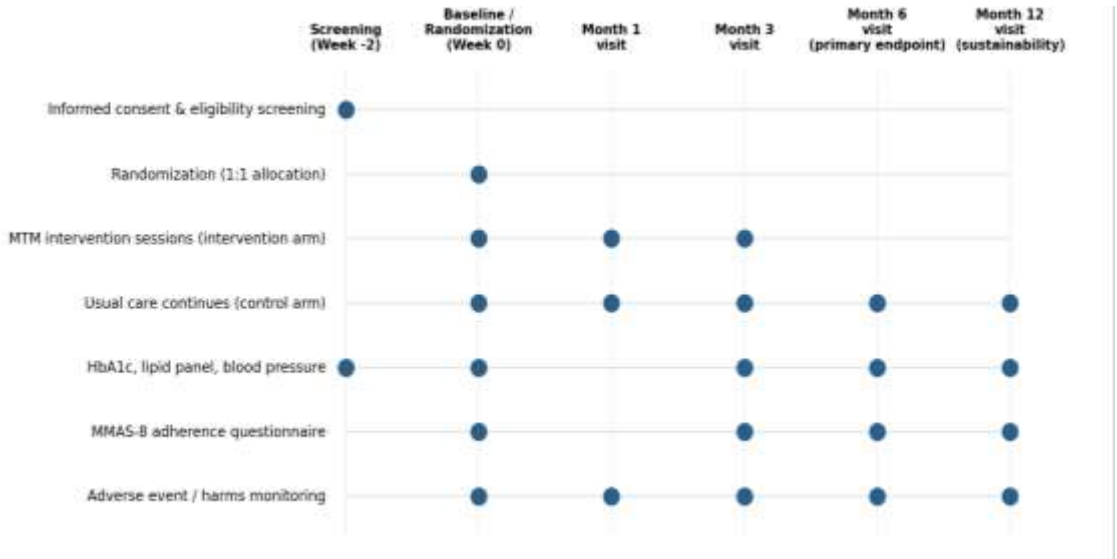

Figure 1. SPIRIT Schedule of Enrolment, Interventions, and Assessments

3.7 Sample Size

The sample size calculation assumes that a 0.5% difference between group means for HbA1c will be clinically meaningful, as this value was recently reported in the most relevant published meta-analysis [8] and was chosen conservatively as being smaller than the difference observed in the literature. With a standard deviation of 1.3 percentage points, comparable to other T2DM outpatient populations [17], two-

sided significance level of 0.05 and a power of 80%, the sample size per group was calculated based on the standard formula for comparing two independent means [17] as detailed in Table 3.

Table 3. Sample Size Calculation Parameters

Parameter	Value	Source/Justification
Minimum clinically important HbA1c difference (Δ)	0.5 percentage points	Conservative threshold relative to pooled SMD of −0.67 reported in [8]
Assumed common standard deviation (SD)	1.3 percentage points	Typical HbA1c variability in outpatient T2DM cohorts
Two-sided significance level (α)	0.05	Conventional threshold
Statistical power (1−β)	80%	Conventional threshold
Formula	n per group = $2(Z(\alpha/2) + Z(\beta))^2 \times SD^2 / \Delta^2$	Standard formula for comparison of two independent means [17]
Calculated n per group (before attrition)	106	$2 \times (1.96 + 0.84)^2 \times 1.3^2 / 0.5^2$
Anticipated attrition at 6 months	20%	Based on retention rates in comparable community-pharmacy intervention trials
Target n per group (after attrition adjustment)	135	106 / (1 − 0.20), rounded up
Total target enrollment	270	135 per arm

In the primary analysis (Section 3.10), between-site clustering is also taken into account, so that the sample size indicated above is the minimum sample size, and the intracluster correlation at the level of the site will be monitored to determine whether the sample size should be adjusted. Figure 2 shows the planned CONSORT participant flow as it moves from enrolment to analysis – observed counts will be added in as they become available as the participants are enrolled.

3.8 Recruitment

Recruitment will be done directly via the pharmacies using the routine prescription pick-up process and through referral from partnering primary care clinics. The number and reasons for non-enrollment will be documented in a screening log, to support the CONSORT flow diagram (Figure 2), and to describe potential selection effects.

3.9 Randomization, Allocation Concealment, and Blinding

The randomization sequence will be a computer-generated permuted block sequence with a size of 4 and 6, and will be randomly varied in each group stratified by site and baseline HbA1c (below 9% vs. 9% or higher), generated by a statistician who was not involved in recruitment or delivery of the intervention. Allocation will be masked by sequentially numbered and opaque sealed envelopes produced centrally or an equivalent central computer-generated envelope system will be used if available. Participants will be enrolled and assigned to intervention per a concealed sequence by the research coordinators who will not be assigned to the pharmacist. To minimize selection bias, the research coordinators not assigned to the pharmacist will enroll participants and assign intervention. For the face-to-face behavioral intervention, the participants and pharmacists cannot be blinded. Laboratory outcome assessment (HbA1c, LDL cholesterol) will be done by staff not involved in allocation, and primary-outcome analysis will be done by an analyst who is not aware of the group assignment in the study (arms coded “A” and “B”) until the end.

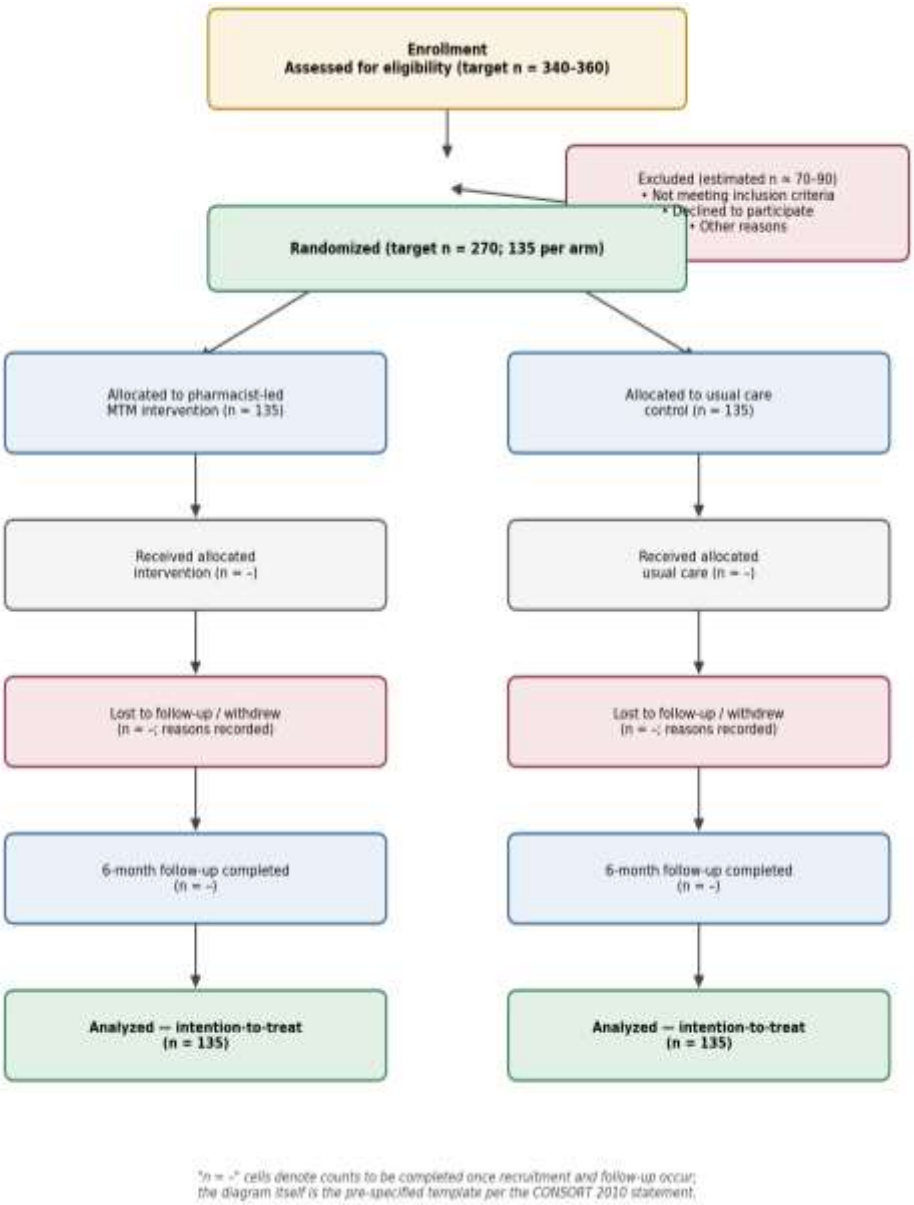

Figure 2. CONSORT Participant Flow Diagram

3.10 Data Collection, Management, and Statistical Analysis

Clinical measures (HbA1c, blood pressure, LDL cholesterol) will be collected via the participant's existing laboratory and clinical care pathways, with trial-scheduled collection, if necessary, where the necessary window measurements have not been completed. The data will be gathered through a structured interview or self-administered questionnaire at each contact, and by electronically extracting pharmacy dispensing records for MPR. Data will be entered into a dedicated electronic case report form with range checks and mandatory field mustering and the data will be role restricted and the data for participant identification will be separate from the data for outcomes and will be connected to each other by a coded study identifier.

The primary analysis will be a mixed-effects linear regression model with fixed effects of treatment group, baseline HbA1c, and randomization stratum and a random effect of the pharmacy site to account for intracluster correlation in a clustered-recruitment trial [18]. The primary analysis is based on the intention to treat principle and includes all randomized patients in the treatment group to which they were assigned, whatever happens. Secondary continuous outcomes (MMAS-8, blood pressure, LDL cholesterol, medication possession ratio) will be analyzed using mixed-effects models that are analogous to the models used for the

primary continuous outcome; and binary outcomes (acute care utilization) with mixed-effects logistic regression. A per protocol sensitivity analysis will be pre-specified to limit the intervention arm to those individuals who have at least 4 contacts out of 5. Multiple imputation under the missing-at-random assumption [19] will be used for missing data, and sensitivity analysis conducted under other missingness assumptions. In view of the explorative nature of secondary endpoints, their interpretation will be descriptive, although a two-sided p-value < 0.05 will be significant.

3.11 Interim Analysis and Data Monitoring

There is no planned formal interim efficacy analysis as the trial is small and the behavioural intervention risk is low. An independent data and safety monitoring function will review safety data that accumulate (severe hypoglycemia and other serious adverse events) at the recruitment point in the middle of the study and has the authority to make an early recommendation for modification if an unexpected safety signal is detected. At pre-specified time points, an independent trial oversight committee (TIC), independent of the investigator team, will review recruitment progress, protocol deviations, and safety data. Fidelity and data quality at the site level will be assessed at each pharmacy randomly on a sample of records at the time of recruitment and at follow-up.

3.12 Harms

All adverse events, in particular hypoglycemic events, will be documented on each occasion of contact and graded for severity and reported to the ethics committee that oversees the trial according to local regulatory requirements. Pharmacological need remains unchanged and thus any underlying diabetes pharmacotherapy is managed by participants' usual treating doctors during the trial; because of the nature of the intervention (behavioural, non-pharmacological), the anticipated harms of the trial are likely to be minimal.

3.13 Ethics, Registration, and Dissemination

This protocol would undergo review and approval by the responsible institutional research ethics committee(s) before enrollment and an amendment would be submitted for review and approval before implementation. All participants will receive written informed consent before any study procedure from trained research coordinators who will provide an information sheet detailing the purpose, procedures, risks, benefits, voluntary nature and right to withdraw from the trial without affecting usual care. All the data collected by the participants will be anonymized with information that enabled the re-identification of the participants kept in separate files and only made available to authorized persons.

In accordance with the guidelines for prospective registration of trials and ICMJE expectation for transparent reporting [20], the trial will be registered in a public trial registry before the first subject is enrolled in the trial. The results will be submitted for peer-reviewed publication and presented at the relevant conferences irrespective of direction and significance. However de-identified results of the aggregate will be shared with participating pharmacies and also, as possible, with participants. The acceptability and comprehensibility of the intervention schedule and outcome measures will be discussed with community pharmacists and patient representatives during final protocol refinement to document consultation and any changes made, before being finalized.

4. RESULTS AND DISCUSSION

4.1 Trial Status and Anticipated Analytic Output

This manuscript outlines the completed trial protocol at the time of writing; as per the prospective SPIRIT-conforming publication [13], [14] no safety, adherence or HbA1c values are available yet. The dates of recruitment and when the protocols had been enrolled and amendments made will be updated in the trial registry and in future publications of this trial, following the ICMJE's reporting standards that require both positive and negative results to be reported completely [20]. The main strengths and weaknesses of

the design, in accordance with CONSORT and SPIRIT guidelines [13], [14], [15] are therefore described here with the results anticipated in the future.

When recruitment and follow-up are completed, the primary analysis (Section 3.10) will provide an estimate of change in HbA1c at 6 months (in the between-group analysis), relative to baseline HbA1c, stratification and accounting for cluster-randomization by pharmacy-site. If a statistically significant and clinically meaningful improvement in blood glucose level was found in the intervention arm (near or at the pre-specified threshold of 0.5 percentage point), against contemporary glycemic-target guidance [21] then pharmacist-led MTM would be considered to be an effective addition to usual care. Subjecting the trial to section 3.13, a null or attenuated outcome would still be informative given the powerfully-designed, adequately powered and pre-registered nature of the trial. The MMAS-8 analysis in parallel with the H2 arm will differentiate between mechanisms of glycemic benefit in the context of adherence measured, as an adherence-mediated mechanism versus other mechanisms (such as more timely intensification of therapy based upon pharmacist-identified DRPs, etc.). The 12 month sustainability analysis will also provide information as to whether effects remain beyond the active intervention period or lessen after pharmacists' contact, which directly impacts the durability of the model of intervention and thus its cost effectiveness.

4.2 Strengths of the Design

Before reaching the results of the design, it is necessary to discuss the following design features: The two primary/secondary outcome design is a common problem in the pharmacist intervention literature because many trials only report one domain of outcomes, which makes interpretation of the role of pharmacist intervention in glucose control difficult since it may have only a modest effect on this outcome [4] or no effect at all [8]. Second, the pre specified 12 month sustainability follow up, three months after the last contact, was incorporated to help differentiate a durable effect from one that was limited to the active period, as indicated in Section 2.4. Third, a cluster-aware analysis at the pharmacy-site level recognises that the counselling systemisation may come from the pharmacist, as well as from the participants, and a naive individual-level analysis would not capture/address this, as the intracluster correlation methods [18] are already well established. Fourth, the intervention is based on a motivational interviewing framework that has been shown to have glycemic and self-management effects in T2DM [11] and will be accompanied by standardized fidelity monitoring, which will help address the reproducibility issues of the previous diverse literature [8].

4.3 Anticipated Limitations

There are also some limitations in the design that were foreseen. Giving the participants and pharmacists both the blind is not feasible because the behavioural intervention is delivered face-to-face, which can increase or decrease engagement/reporting between arms; this is partially reduced by blinded laboratory outcome assessment and blinded primary analysis (Section 3.9). By choosing an assumed effect size lower than the pooled estimate from the most relevant meta-analysis [8] the trial was designed to have a conservative target with a realistic chance of recruitment, although not large enough to detect smaller and possibly relevant effects. The analysis of missing data (following recommended multiple-imputation practice [19]) is based on the assumption that the data are missing at random, but this can only be partially tested; the pre-specified sensitivity analysis for alternative missingness assumptions partially, but not completely, reduces this uncertainty. Lastly, as a limited-multi-site pragmatic trial, generalizability to health systems with materially different scope-of-practice regulations for pharmacists should be taken with a grain of salt due to the reported differences across the country in chronic disease management by pharmacists [4].

4.4 Implications for Practice and Policy

The design decisions have implications for the design and broader measurement of community-pharmacy-based MTM services, even prior to outcome data. The fixed, five-contact schedule, standardized session checklist, and specific pathway for prescriber-to-communication (Section 3.4) operationalizes the

concept of pharmaceutical-care, making it sufficiently specific for a service that can be provided consistently across sites and, if it is found effective, replicated elsewhere without a need to reinterpret a loosely described intervention. In the health care arena, as in the research literature, there has been a reproducibility issue for health systems and payers who are considering reimbursing pharmacist-led services: if a health system delivers a successful service, it is hard to determine if a different health system will produce the same results. This protocol seeks to enhance the internal validity of the current trial by publishing the full intervention script, outcome definitions and analysis plan before enrollment, as well as to make it easier for other investigators and health systems to replicate this trial.

4.5 Relation to Digital and Adjunctive Approaches

No specific smartphone or arm for a digital reminder is included in the protocol because of the earlier-stage evidence for digital-only adherence interventions in T2DM compared to counselling delivered by pharmacists [12]. If the trial shows that the intervention is effective, then a logical next step would be a factorial or adaptive trial to determine whether an electronic supplement to the structured pharmacist contact is effective, rather than a replacement for it: a question this trial is not powered to address, but the infrastructure (electronic case report form, coded identifiers, site-level electronic data pipeline) can be reusable for future trials.

5. CONCLUSION

This protocol details a well-designed, well-powered and pragmatic randomized controlled trial (RCT) to determine whether a pharmacist-led, structured MTM intervention is superior to usual community pharmacy care in the treatment of adults with T2DM with respect to glycemic control and medication adherence. The intervention design directly addresses the three limitations often noted in the pharmacist-intervention literature—single domain outcome reporting, insufficient standardization of interventions, and short-term assessment of the sustainability of effects beyond the active intervention period—by specifying a dual glycemic and adherence outcome structure, intervention schedule, fidelity monitoring, and a cluster-aware analysis plan, while providing a 12-month sustainability follow-up. By publishing the protocol before outcome data are available, in line with the SPIRIT guidelines and ICMJE transparency standards, selective outcome reporting is likely to be minimized and the evaluation of community-pharmacy based chronic disease management is likely to be reproducible. The standardized protocol will help make it easier to replicate and adapt for use in pharmacy practice with various scopes of practice, and will be supported by an expanding evidence base on the role of the pharmacist in chronic disease management, if the trial documents a clinically meaningful and durable benefit. However, no effect would also be an important value-added contribution to the growing literature that is quite heterogenous in terms of design of the intervention and measures of its effects. The results of this trial will help to guide clinical practice guidelines for diabetes care in community pharmacies and design of confirmatory or implementation studies.

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Author Contributions Statement

Name of Author	C	M	So	Va	Fo	I	R	D	O	E	Vi	Su	P	Fu
Abdul Mukit	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓		✓	✓

C : **C**onceptualization I : **I**nvestigation Vi : **Vi**sualization

M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

Conflict of Interest Statement

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Informed Consent

All participants were informed about the purpose of the study and their voluntary consent was obtained prior to data collection.

Ethical Approval

Not applicable.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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