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Optimizing diabetes management interventions for Black and Hispanic adults using the multiphase optimization strategy: Protocol for a randomized mixed methods factorial trial

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Abstract

Background: Black and Hispanic adults with diabetes are more likely to experience diabetes complications and die from diabetes compared to non-Hispanic whites. This disparity may be due to medication adherence being negatively affected by social determinants of health (SDOH) and negative beliefs about diabetes and diabetes medicines. Pharmacist delivered medication therapy management (MTM) improves clinical outcomes. However, pharmacists have limited capacity and expertise to address SDOH barriers and health misperceptions. Supplementing MTM with

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Declaration of competing interest

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Community Health Workers (CHWs) to address these factors may be more effective with potential for implementation.

Aim: To investigate what combination of two possible components, pharmacist delivered MTM and CHWs addressing SDOH barriers and health misperceptions, represents the optimized intervention for Black and Hispanic adults with uncontrolled diabetes.

Methods/design: We will use a 2 × 2 factorial design (MTM, CHW: ON vs. OFF) where participants will be randomized to one of four treatment conditions in a 6-month intervention delivered mostly by phone. We will recruit 376 Black or Hispanic adults with type 2 diabetes and hemoglobin A1C of ≥8 %, a clinical indicator of uncontrolled type 2 diabetes. The primary outcome is A1C measured at 6 months, and at 12 months for sustained change. The secondary outcome is medication adherence. Several psychosocial factors will be examined as potential mediators. An embedded experimental mixed methods approach will be used to obtain participant perspectives through qualitative interviews and integrated to assess intervention acceptability.

Discussion: Our findings will identify the optimized intervention, e.g., comprising MTM or CHW or both intervention components, that effectively and efficiently improves diabetes outcomes among Black and Hispanic adults with uncontrolled diabetes, informing dissemination.

Keywords

Diabetes management; Community health workers; Pharmacists; Mixed methods; Black; Hispanic; Social determinants of health; Multiphase optimization strategy

1. Background

Among US adults, the prevalence of diagnosed diabetes is 12.1 % for Black adults, and 11.7 % for adults of Hispanic origin, compared to 6.9 % for non-Hispanic white adults. [1] Black and Hispanic adults with diabetes are three times more likely to experience diabetes complications compared to non-Hispanic whites and twice more likely to die [2–4]. There are several reasons for these complications and associated disparities. One primary reason is Black and Hispanic adults' lower adherence to diabetes medicines compared with non-Hispanic whites [5–7].

Black and Hispanic adults' ability to adhere to diabetes medicines was found to be negatively affected by exposure to adverse social determinants of health (SDOH), along with having more negative beliefs about diabetes and medicines [8–11]. SDOH are conditions in which people are born, grow, live, work, and age [12]. These circumstances, shaped by the distribution of money, power, and resources are drivers of health inequities—the unfair and avoidable differences in health status. Hence, SDOH barriers are essential intervention targets to achieve health equity and lessen the disproportionate burden of diabetes [12]. Minimizing diabetes-related SDOH factors (e.g., food insecurity) could reduce personal stress, empower patients to engage in self-management, and improve hemoglobin A1c (A1C) in Black and Hispanic adults [13–17].

Negative perceptions about disease and treatment can also be a barrier to diabetes control, as they influence access to adequate, correct information about medication use, and other

diabetes self-management practices [11]. In our prior work, we found that Black adults reported doubts regarding the effectiveness and/or safety of medicines, denial of diabetes diagnosis, fear and frustration about diabetes and taking diabetes medicines, and concerns about medication side effects [18–20].

Addressing health misperceptions through education about diabetes and medicines, and peer-based shared, lived experiences may reduce negative beliefs about diabetes and medicines, increase social support, increase self-efficacy in medication-taking, and reduce medication nonadherence [21]. In our prior study, peer support from a Black paraprofessional led to a reduction in diabetes and medicine misperceptions among Black adults with diabetes and a 9 % reduction in medication nonadherence [21–23]. Diabetes management interventions that minimize SDOH barriers and address health misperceptions among Black and Hispanic adults may facilitate improved medication taking, and other diabetes self-management behaviors.

SDOH has been addressed in several ways including using technology platforms in health and social services systems to screen patients and identify community resources [24,25]. As well, health navigators like Community Health Workers (CHWs) have formal training and professional time to identify and screen for diabetes related SDOH, as well as partner with patients to develop solutions. CHWs are especially prepared to work with adults with diabetes as they can address unmet social needs and increase patients' capacity to focus on diabetes management (e.g., medication adherence) [26]. Prior studies among Black and Hispanic adults with diabetes show CHW involvement can decrease A1C levels by 0.5–0.9 % [13–17].

Several strategies for addressing diabetes medication adherence and glycemic control include the use of education, group sessions on self-management skills, phone coaching sessions, and the incorporation of family members [27]. There is also a clear role for pharmacists. Medication Therapy Management (MTM) [28–30] is an approach in which pharmacists provide enhanced management for patients with complex chronic diseases, such as diabetes. Pharmacists may initiate or modify medication therapy; monitor a patient's response to therapy; and identify, resolve, and prevent medication-related problems [31], which can improve glycemic control. In a longitudinal study of MTM for individuals with diabetes, patients with A1C levels greater than 7 % at baseline had a mean 0.5 % A1C decrease at 6 months, and 0.75 % at 12 months [32,33]. Since 2003, MTM provided by community pharmacists has been a reimbursable service available to eligible Medicare and some State Medicaid enrollees, [34] leading to a greater than two-fold increase of eligible patients receiving MTM from 13 % in 2013 to 35 % of patients in 2016. [35] While pharmacist delivered MTM improves clinical outcomes for Black and Hispanic adults, not all pharmacists are trained in MTM and access is often limited. When MTM is available, pharmacists' generally do not have the flexibility to also screen for SDOH and offer resources or address health misperceptions in a systematic manner, which are other critical components of improving medication adherence and optimizing glycemic control. Providing MTM could help with medication optimization for Black and Hispanic adults with diabetes.

This study aims to investigate whether combining pharmacist delivered MTM with CHWs addressing SDOH barriers and health misperceptions in both English and Spanish would effectively and efficiently promote diabetes management for Black and Hispanic adults with uncontrolled type 2 diabetes. CHWs addressing SDOH barriers and health misperceptions may complement MTM's optimization of medication therapy and reduce diabetes disparities in Black and Hispanic adults. Prior studies have combined CHW and MTM support within clinical healthcare settings and examined its impact among Black and Hispanic adults [36]. However, no study has examined which component, or combination of components, effectively reduce glycemic control and are most cost-efficient.

Trial objective:

The overall goal is to identify an optimized diabetes management treatment package, built for real-world dissemination, for Black and Hispanic adults with uncontrolled type 2 diabetes, using mixed methods. The specific aims of the study are:

Aim 1a: Identify the intervention components, or combination of components (MTM optimizing medication therapy, CHW addressing SDOH and diabetes/medicine misperceptions), that are effective in improving diabetes outcomes.

1b. Identify the intervention components/combinations that are cost-efficient given the available resources.

Aim 2: Evaluate whether the intervention components exert their effects on A1C via the hypothesized mechanisms. Potential mediators include medication optimization, diabetes empowerment, social support, personal stress, and beliefs about diabetes and medicines.

Aim 3: Explore the acceptability of the intervention components/combinations through understanding participant experiences.

2. Methods

2.1. Overview

Using the Multiphase Optimization Strategy (MOST) is key to identifying an effective and efficient (i.e., optimized) diabetes management intervention package offered in English and Spanish for Black and Hispanic adults. MOST is a research framework for determining the optimal treatment package – one that includes only effective components that work well together. Traditional experimental designs typically involve randomized trials that test a package of intervention components against a control or usual care, failing to examine the effects of individual intervention components or determine whether all components are effective when combined [37,38].

2.2. Study design

MOST starts with an efficient optimization randomized control trial (ORCT); e.g., factorial trial) that uses the full sample to examine the main effects of the two levels of each factor (ON vs. OFF) and the interactions of the intervention components [37,39]. In this ORCT, we will use a 2 × 2 factorial experiment to evaluate two intervention components

(MTM optimizing medication therapy and CHW addressing SDOH and diabetes/medicine misperceptions) delivered in English and Spanish for Black and Hispanic adults with uncontrolled type 2 diabetes to identify the effective and efficient intervention versions that can be translated into real-world practice. This design will also allow us to examine the mechanisms of action for each factor (i.e., MTM and CHW). The Enhancing Diabetes Management with Pharmacists and Community Health Workers (ENRxICH) trial is registered at ClinicalTrials.gov Identifier: NCT05912647.

Within this proposed experiment, the main and interaction effects of two intervention components will be estimated. The intervention components target gaps in diabetes management by **(a)** using MTM to provide medication therapy (Factor 1), and **(b)** using CHWs to reduce SDOH barriers to diabetes self-management and address diabetes and medicine misperceptions (Factor 2). (*See* Table 1).

We will use a 2 × 2 factorial design where participants will be randomized to one of 4 treatment conditions, where the usual care group (OFF for all intervention components) will continue their regular interactions with their pharmacist (see Fig. 1).

We will estimate the main effects (i.e., whether ON is more effective than OFF) for each factor as well as the 2-way interaction on A1C at 6 months, *the primary outcome*, and medication adherence as *secondary outcome*. To examine sustained effects, we will assess A1C and medication adherence at 12 months. Finally, we will examine cost as a resource constraint. *Second*, we will evaluate the mechanisms by which MTM optimized medication therapy, and CHW addressed SDOH and misperceptions improved A1C. Hypothesized mediators include medication adherence, increased medication optimization, increased empowerment and social support, and decreased personal stress and negative beliefs/misperceptions about diabetes and medicines. *Third*, at the end of the ENRxICH trial, participant experiences will be explored to inform the selection of the optimal treatment package. This is important to ensure that the intervention components/combination are considered feasible for implementation, practical, and acceptable by Black/Hispanic adults who may use the package in real-world settings. Also, pharmacist's and CHW's perspectives can inform dissemination as they will be interviewed in the study.

We will use an embedded experimental mixed methods approach to obtain participant perspectives to augment the results of the ORCT [40]. This method involves collecting quantitative data in the experimental trial and the qualitative data playing a supplemental role in the design, integrating it to assess intervention acceptability and support the decision making in selecting the optimized treatment package (*See* Table 2) [38]. Merging both the quantitative and qualitative data to allow for meta-inferences and integration may result in the selection of optimized diabetes management treatment packages that are also acceptable to Black and Hispanic adults.

2.3. Participants

Inclusion criteria

1. Adult aged 18–90 with diagnosed type 2 diabetes who self-identify as Black and/or Hispanic
2. Can speak and read English or Spanish.
3. Taking at least one oral or injectable diabetes medicine
4. Have an A1C that is ≥8 % (indicates uncontrolled diabetes) [41] based on a point of care test.
5. Have access to a phone during the study period.
6. Will reside in the geographical area during the study period.

Exclusion criteria

1. Have a caregiver who is the main decision maker in self-management.
2. Participated in a MTM intervention in the previous 6 months.
3. Currently participating in another diabetes self-management program.

2.4. Setting

The intervention will be conducted in two community pharmacy locations within Black and Hispanic communities in a Midwestern State in the United States.

2.4.1. Recruitment: We will use several recruitment strategies including a combination of methods (1) mailed letters; (2) telephone recruitment; (3) personal contacts; (4) posters/flyers; (5) community engagement events.

2.4.2. Screening: Participants will initially complete a phone screen to be evaluated for eligibility based on the inclusion criteria. Participants who qualify based on the phone screen, including self-reporting an A1C of ≥8 %, will be scheduled to attend an in-person screening. At this screening, they will complete a point-of-care A1C test which will confirm their A1C value, as well as complete an informed consent form, and survey.

2.4.3. Randomization: After being screened, providing informed consent, and completing baseline measures, participants will be randomly assigned to one of 4 treatment conditions. Randomized allocation will be stratified by race and ethnicity, in blocks of 4 representing each of the 4 conditions. Within each racial/ethnic group, we will randomly order participants, and following that randomly determined order, assign the first four participants to each of the four treatment conditions, with the conditions assigned in a random order. This process will then be repeated for the next four participants. We will implement a random allocation sequence, which will be concealed until the interventions are assigned. Data collectors assessing the primary outcomes will be blinded to the randomization assignment during the study.

2.4.4. Intervention components of the ENRxICH trial

2.4.4.1. Pharmacist-delivered medication therapy management (MTM). Half of the participants randomized to this condition will engage in 6-month MTM delivered over

the phone with an English/Spanish speaking pharmacist, with a minimum of five MTM sessions. The other half of participants will get usual care where they interact with their pharmacists about their medications with limited potential for a comprehensive medication review, and diabetes management support. The Pharmacy's MTM will include comprehensive medication review and assessment (CMR/A) visits [42]. CMR/A are medication reviews that are provided by the pharmacist to help patients get the best results from medications. An initial CMR/A identifies, resolves, and prevents medication-related problems. A follow up CMR/A monitors/evaluates the patient's response to therapy, including the safety/effectiveness of medications.

2.4.4.2. Community Health Worker addressing SDOH and diabetes/medicine misperceptions. Half of the participants randomized to this condition will meet with a CHW for an initial phone call to understand the context of the participant's SDOH needs. The other half of participants will not receive support from a CHW focused on supporting their diabetes management and social drivers of health and addressing their health perceptions. For those randomized to receive CHW support, using questions from the Health Leads Social Needs Screening Toolkit, the CHW will conduct a brief assessment of the five common SDOH barriers related to diabetes management including (1) food insecurity, (2) transportation, (3) prescription medication assistance, (4) access to diabetes education, and (5) physical activity resources to inform the provision of initial resources at the in-person assessment [43,44] Next, the CHW will meet with the participant for an in-person standardized assessment of SDOH needs. Not all participants will likely need SDOH problem-solving and assistance, but an offer will be made to all participants and a minimum baseline initial phone assessment, and a 2-h in-person contact with a CHW will be required. The study team will consider language preference and/or race/ethnicity, to match the participant with the CHW. After contact has been established, the CHW will continue to call the participant to identify solutions to the SDOH barriers, as needed. During these phone calls to address SDOH, CHWs will also discuss misperceptions using a standardized manual from our prior work [21,45]. They will complete a total of nine sessions related to misperceptions. The first five 15–30-min phone calls will discuss managing diabetes based on standardized focused topics from our evidence-informed peer-support medication adherence interventions [21–23] including diabetes coping, addressing fear, frustration and emotional distress, relationship building with providers – asking questions during visits, discussing diabetes with family/friends, maintaining cultural identity. The remaining four 15–30 min phone calls will allow CHWs to help participants' set goals towards managing diabetes and medicines and offer support for barriers to meeting and maintaining their goals.

2.4.5. CHW qualification: CHWs with prior experience serving Black and/or Hispanic communities, will either have diabetes or a close relationship with someone who has diabetes. They will complete a standardized CHW training program led by a community-based organization.

2.4.6. CHW training: To prepare for their role in delivering the study intervention, CHWs will complete 8 h of training in the following topics: (1) Overview of the study, (2) A community-based ethics training [46], (3) Building relationships training (4) Diabetes

101 refresher training, (5) CHW role in addressing diabetes misperceptions, and (6) study logistics and documentation. As part of their role as a CHW, they are trained in SDOH, problem solving, and helping to find solutions and resources to address SDOH needs. Additional training on the specific SDOH content to cover in the study will be offered. Training on addressing diabetes misperceptions includes using simulated role play activities based on a telephone guide and brief guided conversations scripts, and self-reflections. The training adapted from a training curriculum for Peer Leaders from our prior work will be incorporated into the role of the CHW [21,45,47]. CHWs will be trained in documentation of patient contact, supportive, non-judgmental communication, active listening, goal setting, and providing peer support [21,23,45].

2.4.7. Intervention fidelity

2.4.7.1. Pharmacist MTM. Working with the pharmacy team, we will track the CMR/A content that each pharmacist is completing during the MTM sessions, and the number of hours spent with each patient per session. Pharmacists will also complete the standardized protocol as specified under the CMR/A [42]. As part of completing a CMR/A, there are standard protocols, documentations, and specific checklists to complete including communication with prescribers and follow-ups, etc. Each pharmacist will need to meet the criteria for this standardized process. As well, similar to the standard process for providing MTM, every 6 months, each pharmacist providing MTM will complete a training and practice survey to maintain their credentialing, which ensures that they continue to retain information on the standards of completing MTM.

To ensure those receiving usual care (randomized as OFF) do not also get MTM, we will share a list of those who are randomized to this treatment condition with the pharmacist's conducting MTM. They will reference the list when taking on a new patient and not provide MTM to those patients.

2.4.7.2. CHW addressing SDOH and misperceptions. Addressing SDOH –: The CHWs will have weekly check-ins with a study team member experienced in coaching CHWs and monthly check-ins with a CHW supervisor. The study team member with CHW expertise will also attend the monthly CHW supervisor meetings to ensure that all study objectives are being met. Together, they will use a standardized tool to track contacts, mode of communication with the participant (e.g., Zoom, phone), length of time used for care coordination, and core competency skills areas addressed in the contact. Also, they will capture other information relevant to participant barriers/needs. There will be bidirectional communication between the CHW and the research team to discuss the number of CHW/participant contacts, and/or any issues raised during contacts.

Addressing Diabetes/Medicine Misperceptions –: Weekly team meetings will include CHWs who will report on their activity. All phone calls between CHWs and participants will be audio recorded and randomly assessed for fidelity to the protocol; the PI, study coordinator, research coordinators, and CHWs will discuss the phone calls, creating an opportunity to provide feedback.

2.4.8. Data collection

2.4.8.1. Quantitative Phase. Participants will be asked to complete all assessments for primary and secondary outcomes at baseline, 6 months, and 12 months post-enrollment. At baseline, sociodemographic and clinical information including age, gender, self-reported health status will be collected.

Primary outcome measure: Hemoglobin A1c (A1C), will be measured using the Afinion 2 analyzer, [48] which is a compact, rapid, multi-assay analyzer that provides valuable near patient testing at the point-of-care using a finger stick test.

Secondary outcome measures: Medication adherence, a potential mediator, will be measured by: (1) pharmacy medication refill data, using proportion of days covered [49], medication possession ratio [50], and (2) the Adherence to Refills and Medication-Diabetes scale, a self-report measure [51]. Other potential mediating variables include medication optimization, [36] empowerment (Patient Activation Measure), [52] personal stress (Perceived Stress Scale), [53] medication self-efficacy (PROMIS Self-efficacy measure for managing chronic conditions), [54] diabetes (Brief Illness Perception Questionnaire) [55] and medicine beliefs (Beliefs about Medicines Questionnaire), [56] and social support (Diabetes Care Profile) [57].

Cost measures to be collected include intervention component costs: participant time spent in each intervention/intervention combination, pharmacist time delivering MTM, pharmacy staff time, CHW time in delivering the intervention, health related costs and effectiveness such as cost of care for medication adherence/glycemic control, diabetes medical complications medical costs/events averted costs, and quality-adjusted life years. Other costs include participant time in data collection, cost of supplies and intervention materials, as well as research staff time.

2.4.8.2. Qualitative phase. We will use a purposive sampling strategy to recruit 40 participants, with proportional representation of Black and Hispanic participants. Interviews will initially be completed after the intervention ends with 10 individuals in each of the 4 treatment conditions. After the last participants complete their participation, final interviews will be completed with a new set of 10 individuals from the identified optimized component/combination to inform decision making and feasibility of implementation. We will exclude those unwilling/unable to participate in the interview. Semi-structured 60-min interviews will take place via phone/virtual platform (e.g., Zoom) means. Interview guides will explore intervention acceptability, participant perceptions of the intervention components and combinations, and factors that may influence the feasibility of implementation. All audio-recorded interviews in English and/or Spanish will be transcribed by a bilingual professional transcriptionist, with all personal identifying information removed. A bilingual research team member will verify the transcripts against the audio recordings. As well, CHWs and pharmacists can inform intervention acceptability. Hence, 2–4 CHWs, and 2 pharmacists will participate in a at least one group discussion to provide input on effective intervention elements based on their respective roles. Like the participant interviews, all audio-recorded discussions will be transcribed for analysis.

2.5. Analysis

2.5.1. Optimization and analytic strategy: Optimization will be based on evaluations of effectiveness, cost, and acceptability/feasibility of implementation [38,58]. A mixed effects linear regression model will be used to support estimation of intervention component main effects and their potential interaction. These effects will then be used to estimate an expected outcome ($\hat{Y}$) for each the four different versions of the intervention; we will assume that a decrease of ≥0.6 % in mean A1c represents a clinically meaningful improvement [59]. We will then examine the relative costs of the intervention versions and identify those that are value-efficient using the latest recommendations [60]. We will use data from the semi-structured interviews to explore acceptability of each intervention component/combination including the feasibility for implementation of the identified optimized package. If an intervention does not seem acceptable, we will take that into account in selecting an optimized intervention or return to the preparation phase of MOST to explore more acceptable components.

2.5.2. Quantitative analysis

a. Effectiveness: Mixed effects linear regression models will be used to estimate the main effects of MTM optimizing medication therapy and CHW addressing SDOH and diabetes/medicine misperceptions as well as their potential interaction on the primary outcome, A1C. The primary regression model will also include effects for visit (indicator variables for the two follow-up visits: 6- and 12-months post-randomization) and interactions involving the visit indicator variables. The primary comparisons of interest are tests of the MTM and CHW support main effect at the 6-month post-randomization visit and the MTM and CHW interaction. Similar analyses will be conducted for medication adherence. We will also test for interactions between the treatment condition indicator variables and the two indicator variables. Indicator variables for race/ethnicity will be included as control variables. All analyses will be performed on an intention-to-treat, or as-randomized basis. We will conduct a sensitivity analysis to examine the sensitivity of our findings to a missing at random assumption, especially considering missingness as possibly reflecting more negative outcomes. A nominal p-value of 0.025 will be regarded as statistically significant for the assessment of the two main effects, a nominal p-value of 0.05 will be statistically significant for the assessment of the interaction. Analyses will be in R with lme4 and ordinal packages [61–63]. Expected outcomes will be estimated using the fully interacted model.

b. Value-efficiency: We will assess the cost of our intervention components, including all quantifiable opportunity costs, representative of all groups affected by the intervention. Measures for the analysis include costs for each intervention component, other intervention costs (e.g., research staff time) and health-related cost measures. To calculate the average cost/intervention component, we will use data recorded by the interventionists on the length of time spent on the intervention (e.g., time spent on training, phone calls/home visits, scheduling, and travel). The total cost for each intervention component will be calculated

as the aggregated time costs for everyone involved (including participants). The total cost for each intervention component will be summed for a total program cost, representing the treatment combination of participants who received all intervention components. Since the intervention lasts 6 months (with 12-month data collection), but diabetes requires long-term management, we assume continued addressing of SDOH/misperceptions and estimate ongoing post-intervention costs over 5, 10, and 20 years. To estimate health-related costs and effectiveness, we will use data from the 2019 Medicare Current Beneficiary Survey for medical costs [64] and lifestyle change costs from a cost-effectiveness study of a structured lifestyle intervention in adults with excess weight and type 2 diabetes [65]. Costs will be measured as a total number in all intervention components. Medical costs will determine costs avoided for any procedures, emergency room use, number and length of any hospitalization due to diabetes-related complications. Quality Adjusted Life Years (QALYs) will be estimated based on utility values derived from the SF-36 health survey [66,67], at baseline, 6- and 12-months. The SF-36 will be converted to the preference-based SF-6D [68], which allows the SF-36 to be converted to health state preference values and QALYs. The SF-6D data will be converted into QALYs using the area under the curve method [69]. Intervention component costs, health care costs and QALYs will be discounted at 3 %. We will calculate the long-term medical costs and QALYs of participants in each treatment condition. Total cost for delivering MTM will be calculated by aggregating the cost of pharmacy staff time spent in delivering MTM.

c. Mediator analysis: Mediator analysis will explore mechanisms contributing to changes in A1C. Potential mediation of the impact of MTM and/or CHW support on HbA1c via improvements in hypothesized mediators will be assessed by testing indirect effects between the manipulated factor conditions and outcomes via the hypothesized mediators. We will apply structural equation modeling techniques and use the Model Indirect procedure within Mplus to evaluate indirect effects. This approach allows us to separately quantify the individual contributions of mediators as well as the cumulative effects of multiple mediators.

2.5.3. Sample size justification: Sample size calculations are conservatively based on a two-sample *t*-test for differences in mean A1C at the 6-month follow-up visit and an expected 20 % attrition. Based on data from previous studies, the standard deviation of A1C at the 6-month follow-up visit is approximately 1.88 % [26,70–72]. With a two-sided Type I error rate of 2.5 % (Bonferroni-adjusted for the two primary comparisons), the proposed sample size of 376 participants will provide 80 % power to detect a mean difference in A1C of 0.61 % in CHW support compared to No CHW support (Cohen's d = 0.32); the detectable main effect (0.61 %) is consistent with the magnitude of effects of CHW support seen in prior studies and is clinically relevant [72–74]. As well, the main effect is consistent with the magnitude of effects of Black/Hispanic adults with diabetes receiving MTM compared to no MTM as seen in prior studies [75,76]. The use of a fully crossed and balanced design along with effect coding ensures the same standard errors for estimated interaction effects

as for main effects, yielding equivalent levels of statistical power. From the anticipated main effect estimates, we evaluate power for the testing of indirect effects through Monte Carlo techniques [77]. Assuming an overall sample of 376, and a factor to outcome standardized correlation of $r = 0.15$ (approximate equivalent of d = 0.32), we can evaluate the power of indirect effect sizes using two-tailed tests (alpha = 0.05) using 1000 replications and 20,000 Monte Carlo draws per replication. In evaluating power for a single mediator, we achieve 80 % power in the presence of standardized indirect effects of 0.18, implying ~17 % of total effect being due to mediator. Thus, the proposed sample yields good power for testing mediation. Recruitment will be deemed successful if participants are recruited as planned and attrition is ≤20 %. Our projected attrition rate is, in part, based on similar pharmacy interventions and our team's retention expertise in our trials with Blacks/Hispanics with diabetes.

2.5.4. Qualitative analysis: Directed qualitative content analysis, [78–80] using an inductive approach [81] will be conducted. The 40 transcripts will be split among 3-team members. Each team member will receive training in qualitative data collection and analysis before coding the data. There will be an initial discussion among all coders after a review of 4–5 transcripts, which will be used to develop a codebook. The codebook will guide the next set of analyses and consensus will be used to decide on the final codes and themes. For analysis, (1) the transcripts will be initially read to achieve immersion; (2) data will be read line by line to capture key thoughts; (3) the labels and codes will be created; (4) the themes and categories will be developed and organized; and (5) a model for how themes are linked will be developed [80,82,83]. A comparison of themes across participant responses will explore the similarities, differences, and interconnections across codes and participants. All analyses will occur until data saturation, i.e., when the researcher cannot find new dimensions within the data [84]. To establish rigor of the qualitative data [85], we will use Patton's checklist [86] based on (1) credibility - three study team members will code the transcripts independently – investigator triangulation (i.e., multiple coders involved in the data analysis), and we will member check with participants to confirm if our interpretation is salient/credible – to check for resonance with participant experiences. Results of the analysis will be given to 4 participants per condition as well as the optimal component/combination [87]; (2) confirmability, after coding, similarities and divergences will be discussed. Agreement will be reached on codes before results interpretation. After analysis, data will be discussed in the context of the intervention; (3) transferability [84], we will purposively sample for varied intervention experiences [88]; and (4) dependability–we will create and report a detailed audit trail of our process [89].

3. Conclusion

There are significant diabetes disparities including medication non-adherence, among Black and Hispanic adults. These disparities are likely negatively influenced by SDOH and health misperceptions. Effective interventions for medication management, addressing health misperceptions and reducing SDOH barriers are available, but they do not on their own reduce disparities. Black and Hispanic adults with diabetes would benefit from an optimized treatment package combining effective and efficient interventions that are

translatable to the real world and address diabetes disparities [13–17]. Among a number of intervention strategies that address disparities, this ENRxICH trial will evaluate the individual and combined effects of pharmacist delivered MTM and CHW support for SDOH and misperceptions delivered in English and Spanish. We will identify the optimal of these or their combination to improve diabetes outcomes among Black and Hispanic adults with uncontrolled diabetes.

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Data availability

No data was used for the research described in the article.

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EC*	MTM optimizing Medication Therapy	CHW addressing SDOH and Misperceptions
1	No	No
2	Yes	No
3	No	Yes
4	Yes	Yes

*Experimental Condition

Fig. 1.
Design of Experiment.

Table 1

Factorial experiment study design.

***Participants*:** Black and Hispanics with type 2 diabetes
***Factor 1*:** Pharmacist delivered MTM optimizing medication therapy (ON vs. OFF)
***Factor 2*:** CHW address SDOH and diabetes/medicine misperceptions (ON vs. OFF)
***Primary outcome*:** Hemoglobin A1c (A1C)
***Secondary outcome*:** Medication adherence
***Mediating variables*:** Medication optimization, diabetes empowerment, social support, personal stress, self-efficacy, and beliefs about diabetes and medicines
***Optimization objective*:** To identify the value-efficient intervention that produces a clinically significant reduction in A1C (defined as ≥0.6 %).

Table 2

Investigating how MTM, Addressing SDOH and Misperceptions improves A1C and medication adherence: An Integrated Matrix of an Embedded Experimental Mixed Methods Design.

Phases of the ENRxICH trial	Procedures	Analysis	Expected Outcomes	Point of Integration
1. Quantitative phase Aims: 1. Identify the intervention components/combinations of components that are effective and cost-effective in improving diabetes outcomes. 2. Evaluate whether the intervention components exert their effects on HbA1c via the hypothesized mechanisms.	Randomized factorial ORCT using A1C, surveys, and pharmacy refill data	• Mixed effects linear regression • Mediation analysis	Mean decrease in A1C, and improved medication adherence in the optimized treatment package.	
Qualitative phase Aim: Explore the acceptability of intervention components or combinations of components through understanding participant experiences.	Semi-structured interviews with participants who completed the intervention	• Qualitative content analysis • Analytical strategies for establishing rigor	Participant experiences and perceptions of acceptability.	After the intervention, sample individuals in each experimental condition and optimized component/ combination
Mixed method phase Aim: Further explain the impact of the intervention in the context of participant experiences/ perception of acceptability	Embedding approach using A1C, pharmacy refill, survey, and interview data	• Joint display to merge data findings • Meta-inferences	Aspects of the intervention that contributes to showing its acceptability and feasibility of implementation	