Study Protocol with Statistical Analysis Plan and Informed Consent Form

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Implementation and Assessment of a Medication Therapy Management Program in HIV Patients at High Risk of Adverse Drug Events in ANALYSIS PLAN -INFORMED Khartoum, Sudan

A Three-Arm Randomized Controlled Trial with

Convergent Parallel Mixed-Methods Design

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PHARMACEUTICAL BIOTECHNOLOGY, MOLECULAR PHARMACOLOGY

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Sudan Federal Ministry of Health Ethics: RD/FMOH/144/2020

Study Protocol

1. PROTOCOL SYNOPSIS

Element	Details
Study Title	Effectiveness and Cost-Effectiveness of a Medication Therapy Management Program for HIV Patients at High Risk of Adverse Drug Events: A Three-Arm Randomized Controlled Trial with Mixed-Methods Evaluation in Khartoum, Sudan
Study Design	Three-arm parallel randomized controlled trial (RCT) with embedded convergent parallel mixed-methods evaluation
Study Duration	30 months (6 months recruitment, 24 months follow-up)
Study Sites	Khartoum Teaching Hospital; Omdurman Teaching Hospital; Ibrahim Malik Teaching Hospital (3 sites)
Target Sample	1,149 participants (383 per arm)
Study Arms	Arm 1: Usual Care (UC); Arm 2: Basic MTM (BMTM); Arm 3: Enhanced MTM (EMTM)
Primary Outcome	Medication adherence: Proportion of Days Covered (PDC) ≥95% at 6 months
Key Secondary Outcomes	PDC at 24 months; viral suppression; CD4+ count change; adverse drug events; drug-related problems; QALYs; cost-effectiveness
Quality of Life Instrument	EQ-5D-: confirmed as administered version
Economic Evaluation	Trial-based cost-effectiveness analysis; WTP = USD 750/QALY (Sudan GDP threshold)
Analysis Framework	Intention-to-treat (ITT) with multiple imputation for missing data (MAR assumption)
Ethics Approval	USM JEPeM; Sudan Federal Ministry of Health
Registration	ClinicalTrials.gov (NCT ID not yet assigned) ANALYSIS PLAN -INFORMED

2. BACKGROUND AND RATIONALE

Sudan bears a disproportionate burden of HIV in North Africa, with an estimated 55,000 people living with HIV (PLHIV) and an antiretroviral therapy (ART) coverage of approximately 47% (UNAIDS, 2023). Among those on ART, adherence rates remain suboptimal, and the prevalence of adverse drug events (ADEs) driven by polypharmacy, drug-drug interactions, and immune reconstitution inflammatory syndrome represents a major clinical challenge at Khartoum's three principal HIV treatment centers.

Medication Therapy Management (MTM) is a structured, pharmacist-led service model encompassing comprehensive medication review (CMR), a personal medication record (PMR), a medication action plan (MAP), interventions and referrals, and documentation and follow-up. MTM has demonstrated effectiveness in improving adherence, reducing drug-related problems (DRPs), and lowering healthcare costs in multiple chronic disease settings (Bluml, 2005; Smith et al., 2013; Isetts et al., 2008). However, evidence for MTM effectiveness in HIV care in sub-Saharan Africa and the Arabic-speaking Middle East/North Africa (MENA) region remains limited, and no cost-effectiveness analyses using QALY-based methods have been published for this population.

This protocol describes a three-arm RCT to evaluate two intensity levels of MTM (Basic and Enhanced) against usual care in HIV patients at high risk of ADEs at three Khartoum teaching hospitals, with an embedded mixed-methods component to understand implementation barriers and facilitators using the Consolidated Framework for Implementation Research (CFIR; Damschroder et al., 2009, 2022).

3. STUDY OBJECTIVES

3.1 Primary Objective

To evaluate the effectiveness of two levels of Medication Therapy Management intervention (Basic MTM and Enhanced MTM) compared to usual care in improving medication adherence (PDC ≥95%) among HIV patients at high risk of adverse drug events over a 24-month follow-up period.

3.2 Secondary Objectives

- To compare medication adherence (mean PDC and PDC ≥95% threshold) at 6 months (primary) and 24 months between the three arms

- To evaluate the effect of MTM on viral suppression (<200 copies/mL) at 6 and 24 months
- To assess CD4+ lymphocyte count changes from baseline to 24 months
- To compare the incidence of adverse drug events and drug-related problems between arms
- To assess health-related quality of life using the EQ-5D-3L instrument []
- To evaluate patient satisfaction with pharmaceutical care services
- To measure treatment self-efficacy using the HIV-ASES scale
- To conduct a trial-based cost-effectiveness analysis with pre-specified WTP threshold
- To explore implementation barriers and facilitators using the CFIR framework (qualitative component)

4. STUDY DESIGN

This study employs a three-arm parallel-group randomized controlled trial with equal allocation (1:1:1) stratified by study site and baseline viral suppression status (suppressed: <200 copies/mL vs. unsuppressed: ≥200 copies/mL). An embedded convergent parallel mixed-methods component collects qualitative data through focus group discussions (FGDs) and in-depth interviews (IDIs) concurrently throughout the 24-month follow-up period, with integration at the analysis stage.

4.1 Study Timeline

- Months 1–6: Recruitment and baseline assessment
- Months 1–30: MTM intervention delivery (ongoing)
- Month 6: Primary outcome assessment (PDC ≥95%)
- Months 12 and 18: Interim assessments
- Month 24: Outcome assessment (all secondary outcomes)
- Months 18–24: Qualitative data collection (FGDs and IDIs)
- Months 25–30: Data analysis, integration, and reporting

5. SAMPLE SIZE AND RANDOMISATION

5.1 Sample Size Calculation

Sample size was determined using G*Power 3.1 (Faul, Erdfelder, Lang, & Buchner, 2007). For a chi-square goodness-of-fit test comparing three independent proportions ($\alpha = 0.05$, two-sided; power = 0.80; expected PDC ≥95% rate of 53% in UC arm and 70% in MTM arms; effect size w = 0.17; df = 2), the minimum required sample size was n = 294 per arm (total N = 882).

Attrition Adjustment: Based on an expected attrition rate of 23.4% over 24 months (based on a review of comparable HIV adherence RCTs in sub-Saharan Africa reporting 20–25% dropout over

2 years), the inflation factor is 1/0.766 = 1.305. Final target: n = 294 × 1.305 = 383.6, n = 383 per arm (total N = 1,149).

5.2 Enrolment and Retention

Target enrolment: 383 per arm (1,149 total). Actual enrolment from participant master list: UC 380, Basic MTM 382, Enhanced MTM 387 (total 1,149). Randomization lists were generated for 383 per arm; minor differential enrolment reflects participant flow at site level.

5.3 Randomization and Allocation Concealment

Randomization was performed using a computer-generated random number sequence prepared by an independent statistician. Block randomization with variable block sizes (blocks of 6, 9, and 12) was used within each stratum (site × viral suppression status = 3 × 2 = 6 strata). Allocation concealment was achieved using sequentially numbered, sealed, opaque envelopes that were opened only after baseline assessments were completed.

Blinding: Due to the nature of the MTM intervention, blinding of participants and pharmacist-investigators to treatment allocation is not feasible. Outcome assessors (laboratory staff for viral load and CD4 tests) are blinded to allocation. Statistical analysis is performed by an independent statistician blinded to arm allocation.

6. STUDY INTERVENTIONS

6.1 Arm 1 — Usual Care (Control)

Participants receive standard HIV care as provided by the treating HIV clinic team without structured pharmaceutical services. This includes routine ART dispensing by pharmacy staff, standard physician consultations, and laboratory monitoring (viral load every 6 months; CD4 annually). No pharmacist-led medication review, adherence counseling, or DRP identification is provided. Participants are not denied any care they would otherwise receive.

6.2 Arm 2 — Basic MTM (BMTM)

Participants receive all usual care elements plus a structured Basic MTM service comprising: (1) Comprehensive Medication Review (CMR) at enrolment and every 6 months; (2) a Personal Medication Record (PMR) provided and updated at each visit; (3) a Medication Action Plan (MAP) co-developed with the patient; (4) face-to-face MTM visits at months 0, 6, 12, 18, and 24 (45–60 minutes each); and (5) telephone follow-up calls at months 3, 9, 15, and 21 (15–20 minutes

each). DRP identification and pharmacist-to-prescriber communication are conducted at each CMR.

6.3 Arm 3 — Enhanced MTM (EMTM)

Participants receive all Basic MTM components plus enhanced elements: (1) more frequent face-to-face visits (monthly in months 1–3, then every 3 months); (2) home visits or additional telephone contacts for high-risk patients; (3) structured peer support group sessions; (4) adherence aids (pill organizers, medication reminder tools); and (5) enhanced prescriber communication including participation in multidisciplinary team meetings. EMTM pharmacists complete additional training in motivational interviewing and CFIR-informed implementation strategies.

7. DATA COLLECTION INSTRUMENTS

7.1 Primary Adherence Measure

Proportion of Days Covered (PDC): Calculated from pharmacy dispensing records as the number of days with medication on hand divided by the number of days in the observation period. The PDC ≥95% threshold is used as the dichotomous primary outcome consistent with the literature (Nau, 2012). The mean PDC is analyzed as a continuous secondary outcome.

- AACTG Adherence Questionnaire: validated self-report adherence scale; 4 items; administered at all time points
- MARS-5 (Medication Adherence Report Scale): 5-item validated scale; primary validation: Horne & Weinman (1999)
- Visual Analog Scale (VAS): 100mm horizontal scale for patient-rated adherence

7.2 Clinical Outcome Measures

- Viral load (HIV RNA): plasma viral load by PCR; suppression defined as <200 copies/mL; collected at baseline, 6 months, and 24 months
- CD4+ lymphocyte count: absolute count by flow cytometry; collected at baseline and 24 months
- Adverse drug events (ADEs): identified using the Naranjo Adverse Drug Reaction Probability Scale (Naranjo et al., 1981); classified as definite/probable/possible/doubtful
- Drug-related problems (DRPs): identified and classified using the modified PCNE Drug-Related Problem Classification System v9.1 (Pharmaceutical Care Network Europe, 2020)

7.3 Patient-Reported Outcome Measures

Quality of Life Instrument:

- EQ-5D-3L: five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression); three levels each; scored using Dolan (1997) UK tariff; index range -0.594 to 1.000; EQ VAS 0–100
- HIV-ASES (HIV-Related Self-Efficacy Scale): 12-item validated scale measuring HIV treatment self-efficacy
- Patient Satisfaction Survey: 10-item investigator-developed scale; 1–5 Likert scale

8. STATISTICAL ANALYSIS PLAN

8.1 Analysis Population

The primary analysis follows intention-to-treat (ITT) principles, including all randomized participants regardless of protocol adherence. Missing data will be handled using multiple imputation by chained equations (MICE), with m = 20 imputed datasets, assuming missingness is missing at random (MAR). A per-protocol (PP) sensitivity analysis will include only participants who complete ≥80% of scheduled MTM visits and have complete outcome data.

8.2 Primary Outcome Analysis

PDC ≥95% at 6 months will be compared across the three arms using a Pearson chi-square test (df = 2). Post hoc pairwise comparisons will apply a Bonferroni correction ($\alpha = 0.017$ per comparison). Adjusted odds ratios (ORs) for PDC ≥95% achievement will be estimated using multivariable logistic regression controlling for: age, sex, education level, baseline viral suppression, baseline CD4 count, baseline PDC, and study site.

8.3 Secondary Outcome Analyses

- CD4 count change: Linear mixed-effects model (LME) with random intercept per participant, fixed effects for time, arm, and time-by-arm interaction; ANOVA as sensitivity check
- Viral suppression: Chi-square at 6 and 24 months; logistic regression for adjusted ORs
- ADEs and DRPs: Chi-square for proportions; negative binomial regression for count data
- EQ-5D-3L utility: LME for repeated measures; QALY calculated by AUC method
- Kaplan-Meier analysis: Time-to-first-adherence-failure, defined as first PDC measurement <80% after initial achievement of PDC ≥95%
- Subgroup analyses: viral suppression status × treatment arm interaction test; no adjustment for multiple testing in subgroups (exploratory)
- ICC for site effect: calculated and reported; if ICC >0.05, design effect adjustment applied

8.4 Software

IBM SPSS Statistics v28 (IBM Corp., Armonk, NY); R version 4.3.0 with packages: mice, lme4, survival, boot; Stata 17 for sensitivity analyses. G*Power 3.1 (Faul et al., 2007) for power calculations.

9. ECONOMIC EVALUATION

9.1 Analysis Type and Perspective

Trial-based cost-utility analysis (CUA) from a healthcare system perspective. The analysis follows CHEERS 2022 reporting standards (Husereau et al., 2022). The time horizon is 24 months, consistent with the RCT follow-up period.

9.2 Costs

- Direct healthcare costs: ART medications, non-ART medications, laboratory tests, clinic visits, hospitalization, and emergency care
- Intervention costs: pharmacist time (staff costs), training, materials, telephone calls
- Unit costs: derived from Khartoum government hospital price schedules and National AIDS Control Program formulary (price year: 2022; currency: USD)
- Costs reported in USD at 2022 prices; no conversion required (denominated in USD)
- Discount rate: 3.5% per annum applied to costs and QALYs beyond the first year of follow-up (NICE, 2022)

9.3 Outcomes

Quality-adjusted life years (QALYs) estimated from EQ-5D-3L utility scores using the area-under-the-curve (AUC) method: QALY = [(U_baseline + U_6m)/2 × 0.5] + [(U_6m + U_24m)/2 × 1.5]. EQ-5D-3L utility values derived using the UK tariff (Dolan, 1997).

9.4 Willingness-to-Pay Threshold

Primary WTP threshold: USD 750/QALY (one times Sudan GDP per capita, World Bank 2022 estimate). The threshold follows the WHO-CHOICE guidance for low-income countries (Bertram et al., 2016; Ochalek et al., 2018).

- Sensitivity analyses at: USD 375/QALY (0.5 × GDP); USD 750/QALY (primary); USD 1,500/QALY (2 × GDP)
- Probabilistic sensitivity analysis (PSA): 10,000 Monte Carlo simulations; costs from gamma distribution; utilities from beta distribution
- Cost-effectiveness acceptability curve (CEAC) presented for both MTM arms vs UC

- Incremental cost-effectiveness ratios (ICERs) with bootstrapped 95% confidence intervals (10,000 replications)

10. QUALITATIVE METHODS COMPONENT

The qualitative component follows Braun and Clarke (2006) six-phase thematic analysis, guided by the Consolidated Framework for Implementation Research (CFIR; Damschroder et al., 2009, 2022) as the a priori theoretical lens. Data collection uses semi-structured in-depth interviews (IDIs) and focus group discussions (FGDs) with three purposively sampled cohorts: HIV patients (IDIs, n≈22), healthcare providers (FGDs, n≈14), and Patient Support Association (PSA) members (FGDs, n≈25).

Data collection and analysis were conducted in parallel with the RCT (convergent parallel design; Creswell & Plano Clark, 2018). Thematic saturation was monitored across successive interviews. NVivo version 12 was used for data management and coding. Inter-rater reliability was assessed by double-coding a 25% subsample of transcripts; Cohen's kappa is reported.

Reflexivity: The principal investigator is a clinical pharmacist embedded in the study setting. A reflexivity statement addressing the potential influence of the researcher's positionality on data collection and interpretation is included in the qualitative findings section.

11. ETHICAL CONSIDERATIONS

- Ethics approval: USM Human Research Ethics Committee (JEPeM); Sudan Federal Ministry of Health Research Ethics Committee
- Written informed consent: obtained from all participants in Arabic (primary language) with certified English translation
- Confidentiality: participant data de-identified; coded identifiers only in all data files
- Right to withdraw: participants may withdraw at any time without affecting their clinical care
- Protocol deviation: The EQ-5D-3L instrument was administered instead of the EQ-5D-5L specified in the original protocol. This deviation was documented using a protocol deviation form and is described in Section 7.3.
- Data monitoring: The Trial Steering Committee reviewed study progress and data annually. No formal interim analyses or stopping rules were planned because the study evaluated a low-risk pharmacist-led behavioral intervention.

12. Informed Consent Form (English and Arabic)

12.1 Informed Consent Form (English)

Research Title: IMPLEMENTATION AND ASSESSMENT OF A MEDICATION THERAPY MANAGEMENT PROGRAM FOR HIV PATIENTS AT HIGH RISK OF ADVERSE DRUG EVENTS IN KHARTOUM, SUDAN

Researcher's Name: NADA ABDELRAHMAN MOHAMED IBRAHIM

To become a part of this study, you or your legal representative must sign this page. By signing this page, I am confirming the following:

- I have read all of the information in this Patient Information and Consent Form, including any information regarding the risk in this study, and I have had time to think about it.
- All of my questions have been answered to my satisfaction.
- I voluntarily agree to be part of this research study, to follow the study procedures, and to provide necessary information to the doctor, nurses, or other staff members, as requested.
- I may freely choose to stop being a part of this study at any time.
- I have received a copy of this Participant Information and Consent Form to keep for myself.

Participant Name: _____

Participant I.C No.: _____

Signature of Participant or Legal Representative: _____

Date (dd/MM/yy): _____ / _____ / _____

Name of Individual Conducting Consent Discussion: _____

Signature of Individual Conducting Consent Discussion:

_____

Date (dd/MM/yy): _____ / _____ / _____

Name & Signature of Witness: _____

Date (dd/MM/yy): _____ / _____ / _____

12.2 Informed Consent Form (Arabic)

نموذج الموافقة المستنيرة

عنوان البحث :تنفيذ وتقييم برنامج إدارة العلاج الدوائي للمرضى المعرضين لمخاطر الأحداث السلبية للدواء في الخرطوم، السودا
ن **اسم الباحث :**ندى عبد الرحمن محمد إبراهيم

لكي تصبح جزءًا من هذه الدراسة، يجب عليك أو ممثل قانوني توقيع هذه الصفحة. من خلال توقيع هذه الصفحة، أؤكد ما يلي:

- لقد قرأت جميع المعلومات في نموذج معلومات المريض والموافقة هذا بما في ذلك أي معلومات تتعلق بالمخاطر في هذه الدراسة وكان لدي الوقت للتفكير فيها .
- تم الرد على جميع أسئلتي بما يرضيني.
- أوافق طواعية على أن أكون جزءًا من هذه الدراسة البحثية، وأن أتبع إجراءات الدراسة، وأن أقدم المعلومات الضرورية للطبيب أو الممرضات أو أعضاء الفريق الآخرين، حسب الطلب.
- يمكنني بحرية اختيار التوقف عن المشاركة في هذه الدراسة في أي وقت.
- لقد تلقيت نسخة من نموذج معلومات المشارك والموافقة هذا للاحتفاظ بها لنفسي.

اسم المشارك:

رقم هوية المشارك:

توقيع المشارك أو الممثل القانوني:

التاريخ)يوم/شهر/سنة(:

اسم الشخص الذي أجرى مناقشة الموافقة:

التاريخ)يوم/شهر/سنة(:

اسم وتوقيع الشاهد :

التاريخ)يوم/شهر/سنة(:

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