Digital Health Adherence Companion Study for Tetrathiomolybdate (TM) plus Capecitabine in Triple-Negative Breast Cancer

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Background

Copper depletion therapy with **oral tetrathiomolybdate (TM)** is designed to complement standard adjuvant therapy for **high risk for relapse triple negative breast cancer (TNBC)** by overcoming TNBC resistance mechanisms. In a previous pilot phase 2 clinical trial of TM in 75 breast cancer patients, TM was safe, well tolerated and event-free survival (EFS) for TNBC pts is 88% for high-risk adjuvants (stage 3 breast cancer) and 59.3% for stage 4 NED TNBC at a median follow-up of 10.4 yrs.[1] The dosing of TM requires an induction and maintenance phase with subsequent monitoring of ceruloplasmin and absolute neutrophil counts (ANC).

- Several studies have reported on adherence rates for oral anticancer medications, with prior breast cancer trials having adherence rates of 78% across all cycles.[2]
- In studies with electronic pill cap monitoring systems, reported adherence with oral chemotherapy regimens is on average 85-89%. However, 17% of patients were <80% adherent.[3-4]
- Diaries and paper logs are subject to manipulation and errors for medications where dosing schedules are frequently modified, while micro electric event monitoring systems are not feasible in real-word practice beyond clinical trials.
- Satisfaction with clinician communication and treatment and reduced burden to others have been reported as factors associated with improved adherence to oral chemotherapy. Higher cancer-related symptom severity is associated with lower adherence.[3-4]

Strategies to Measure Adherence to Oral Chemotherapy



Aim: This **trial in progress** aims to evaluate whether a digital mobile application can improve adherence to TM for patients with high risk for relapse TNBC. This is a **companion study for clinical trial NCT06134375**.

Methods

High Risk for Recurrence TNBC
(RCB score 2-3 or node positive after neoadjuvant therapy)

Phase 1b study at Dartmouth and NYU (n = 6 to 18)
Capecitabine + TM + Pembrolizumab
Goal ceruloplasmin: 15-19 (3 years)

Dose Level -1	Dose Level 1	Dose Level 2
Induction: 100 mg/day Maintenance: 80 mg/day	Induction: 140 mg/day Maintenance: 100 mg/day	Induction: 180 mg/day Maintenance: 100 mg/day

Phase 2 study (n = 186)

Arm 1	Arm 2
Capecitabine +/- Pembrolizumab	Capecitabine + TM (3 years) +/- pembrolizumab

Primary Endpoint: Distant relapse free survival
Secondary Endpoints: Overall survival, patient reported outcomes, medication adherence, serial biomarkers (VEGFR2+ EPCs, LOXL-2, ctDNA)

Figure 1. Phase 1b/2 Study Design. Patients will receive TM with capecitabine and pembrolizumab in 20 mg capsule increments, with daily doses up to 180 mg during the induction phase (first 6 months) and 100 mg during the maintenance phase (subsequent 30 months) in 28-day cycles. Doses are divided into capsules taken between one and three times daily.

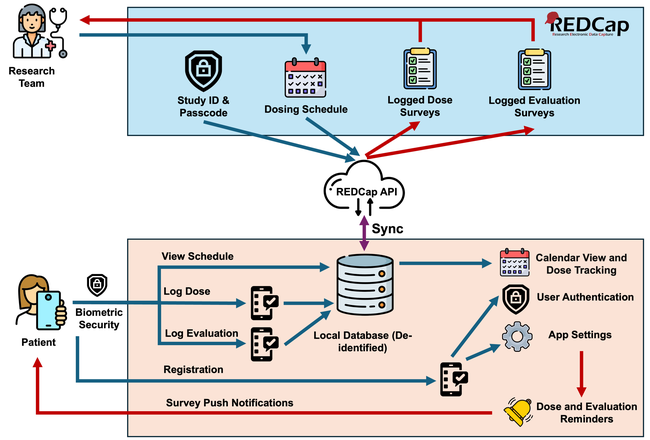


Figure 2. Mobile Application Data Flow Diagram. Study participants register for the study companion mobile app using their study ID and passcode. No other personal identifiable information is stored in the app to protect user data. Participants can easily view and access their dosing schedule in REDCap as it is updated in real time and log doses taken using in-app surveys. Reminder notifications are sent on the user's phone at user preferred times to take each dose. Evaluation and patient-reported outcome surveys are sent to the user periodically.

App Design and User Interface

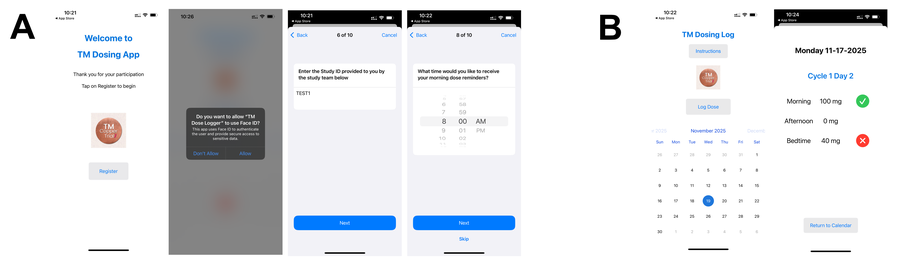


Figure 3. App Registration and Dosing Calendar Interface. A) App requires registration with unique study ID and 32-digit unique passcode after which biometric authentication is required for daily app access. Patients can select notification times they prefer. **B)** Simplified interface displays calendar on main app screen. Selecting a date shows the dosing schedule for each day, synced in real time with any changes made by study team in REDCap. Logged and missed doses are shown to the user.

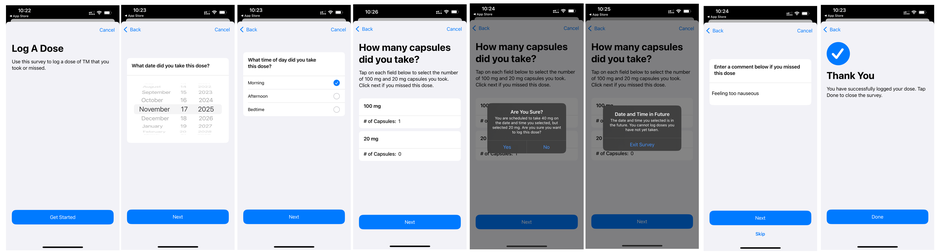


Figure 4. Dose Logging Survey. Tapping on a dose reminder notification opens a survey for logging doses of TM. Users enter the date and time, as well as the amount of each capsule taken, and reasons for any missed doses. Participants are prompted to verify any entries that don't match the dosing schedule in REDCap. Doses must be logged within each calendar day to prevent data manipulation or incorrect data entry. Surveys are logged directly in REDCap and status bar displays when users have not logged 3 consecutive doses.

Statistical Analysis Plan

- Expected sample size of 186 patients with accrual rate of 5 patients per month.
- Usability of the mobile app for daily use and patient satisfaction will be assessed with the **mHealth App Usability Questionnaire** during Cycles 1, 2, and 4.
- Adherence will be measured as number of doses logged within 24 hours of scheduled time for each cycle and across entire three-year study period. Adherence rates will be compared with patients using paper logs and prior reported data using linear mixed models.
- A multivariate regression analysis will be used to evaluate predictors of adherence, including associations with patient reported outcomes (oral, gastrointestinal, cutaneous, neurological, and treatment-related symptoms) measured every 4 months.

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