Statistical/Programming Plan for Cue Reward Trial Analysis

Protocol Version Date: 2022-12-16

1. **Title:** Medication Adherence Patterns in Rheumatic Diseases: A Behavioral Trial: **Phase 2 trial results**

2. **Core research team**
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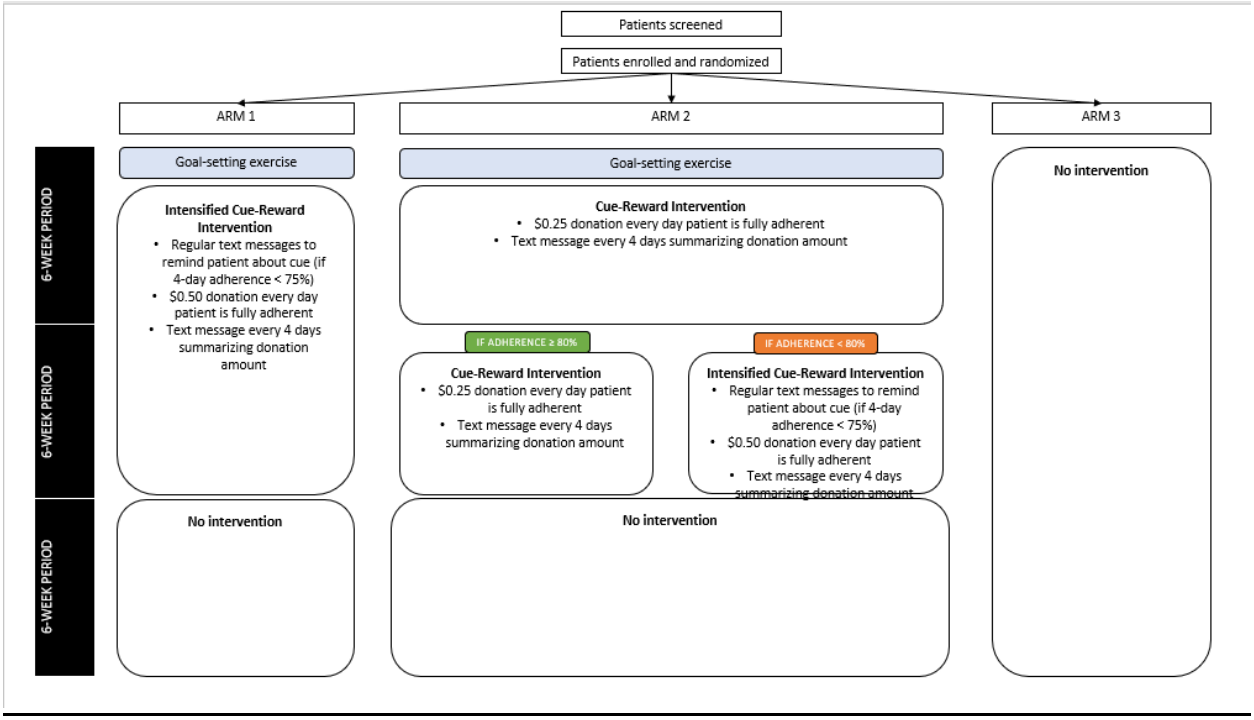
3. **Aim(s): To determine whether strategies that couple context cues and rewards improve adherence to medications**

4. **Data source:**
   a) REDCap data for 56 consented patients (20 = in Adaptive intervention; 18 = in Non-Adaptive Intervention; 18 = in Control) – one dataset
   b) Pillsy pill bottle adherence data for 56 patients - there are N= 352 daily 000_Pillsy files spanning the length of the trial
   c) IRB: 2020P003826
   d) NIA (NIH) funded P30

5. Overall trial diagram:



6. Cohort Identification

6.1 Cohort Summary

There will be 1 cohort formed at the **patient level**.

Each patient should already be identified with the following in the REDCap dataset:

e) Patient Study ID (i.e., Record_id)

f) Arm (arm) (0 = Control, 1 = Non-adaptive intervention, 2 = Adaptive intervention)

6.2 Important steps for cohort formation

6.2.1 Eligible study entry dates/definitions and the corresponding variable names in REDCap.

a) **Screening date:** Date each patient was screened for eligibility for the study and began being contacted for enrollment. (mail_date)

b) **Enrollment date:** Date each patient was enrolled and consented into the study. (date_consent)

c) **Index date**: Each patient began receiving the intervention (either of the text messaging interventions or control). (start_date)

d) **Intervention Completion date:** Index date (inclusive) to 12 weeks beginning on the index date (intervention_date)

e) **Follow-up period**: Index date (inclusive) to 18 weeks beginning on the index date for primary adherence and secondary outcomes.

6.2.2 Specify inclusion criteria for cohort entry and define the index date

Patients are already identified by their study ID (56 patients altogether). The index date is the first day of intervention ("start_date" in REDCap).

7. Variables

7.1 Exposure-related variables:

Patient-level cohort: Within this cohort, please measure and provide the following variables at the patient level:

a) Using the **REDCap file:**
   - Patient demographics:
     - Age (age_years, age), numeric. Please also calculate using dob and start_date
     - Sex (sex)
       - 0 = Not listed
       - 1 = Female
       - 2 = Male
     - Sex if Sex is not listed (sex_other)
     - Race/ethnicity (self reported)
       - 1 = White
       - 2 = Black or African American
       - 3 = American Indian/ Alaska Native
       - 4 = Asian
       - 5 = Native Hawaiian or Other Pacific Islander
       - 6 = Hispanic/Latinx
     - Education level (education):
       - 1 = Less than high school diploma
       - 2 = High school diploma
       - 3 = Some college
       - 4 = College degree
       - 5 = Graduate degree
     - Marital status (marital)
       - 1 = Married
       - 2 = Living with partner/ Domestic partnership
       - 3 = Widowed
       - 4 = Divorced/ Separated
       - 5 = Never married/ Single
     - Employment Status (employment)
       - 1 = Employed
       - 2 = Job seeking

- 3 = Not job seeking
- 4 = Retired
- 5 = Disabled

▪ Income (self-reported) (income)

- 1 = Less than $20,000
- 2 = $20,000 to $34,999
- 3 = $35,000 to $49,999
- 4 = $50,000 to $74,999
- 5 = $75,000 to $99,999
- 6 = Over $100,000
- 7 = Prefer not to say

- Number of self-reported medications on a daily basis (num_meds_daily)
- Number of self-reported medications on a weekly basis (num_meds_weekly)
- Recruitment method (rec_type)
  - 1 = PCP
  - 2 = Rheumatology
- Baseline Uric acid (ua_baseline) used for the study, numeric
- Baseline Uric acid date (ua_baseline_date)
- Baseline Uric acid stratum (ua_stratum)
  - 1 = 6-8 mg/dl
  - 2 = >8 mg/dl
- Arm (arm):
  - 0 = Control,
  - 1 = Non-adaptive intervention,
  - 2 = Adaptive intervention
- Number of prescribed study medications (bottles), numeric
- Medication names (bottle_1_med, bottle_2_med, bottle_3_med)

7.2 Baseline Medication Use Questionnaire:

- 3-item questionnaire: Please perform a linear transformation of the following three variables to a scale of 100 and take the mean of the three for each patient, for those with baseline survey data:
  - missed_doses: numerical value, 0-30. For each day missed, calculate the percentage of days taken out of 30 (e.g. missed_doses=2 → 28/30 = 93.33)
  - medication_supposed :
    - 1=Never → 0
    - 2=Rarely → 20
    - 3=Sometimes → 40
    - 4=Usually → 60
    - 5=Almost Always → 80
    - 6=Always → 100
  - meds_good_job:
    - 1=Very Poor → 0
    - 2=Poor → 20
    - 3=Fair → 40

        - 4=Good → 60
        - 5=Very Good → 80
        - 6=Excellent → 100
      - Please generate a flag for missing any one of these fields (missed_doses, medication_supposed, meds_good_job)
  - Automaticity score categories (automaticity): Present the scores for the 4 questions – automaticity_1_end to automaticity_4_end.
    - 0=No
    - 1=Yes
- Routine related questionnaire
  - Score the following from 1 (Not at all) to 7 (Very much so): routine, same_time, continue_way, take_same_place, take_right_before, take_water, take_same_cup, keep_same_place
- Perception related questionnaire
  - Score from 1 (Strongly Disagree) to 5 (Strongly Agree) the following: regular_apts, tx_plan_difference, med_help_control, prescribed_take_daily, not_taking_effect, feel_well_stop, live_long, control_gout, gout_better_worse, actions_effect

7.3 Baseline Gout Questionnaire

- gout_1 (1 = Yes, 0 = No)
- gout_2 (1 = Yes, 0 = No)
- gout_3 (1 = Yes, 0 = No)
- gout_4 (Score from 1 to 10)

8. Outcome variables and study follow-up:

A) Primary Outcome (Average daily adherence):

For each patient, please measure the following outcomes beginning on the index date:

a) Follow-up period for each patient
   1. Some patients may not have a full 18 weeks of follow-up. This is based on the time between the index date (start_date) and the end date (study_date) or (withdraw_date) whichever is earlier in REDCap. Please provide the number of days between the index date and the end date in REDCap.

b) Calculate daily adherence during the follow-up period (adh_daily), using the available time stamps from the 352 daily **Pillsy files** merged with the **REDCap file:**
   1. Daily adherence values are calculated from Pillsy files, while date information should be taken from REDCap file.
   2. Medications are named using "Medication # QD/BID" (drugName). If name includes "QD", count as 1 expected daily dose; if name includes "BID", count as 2 expected daily doses.
   3. Time stamps (eventTime) within 3 hours of each other (e.g. 9:00am and 11:59am) should be collapsed into one dose. There will likely be multiple time stamps for each opening, but they should be counted as one dose.
   4. Time stamps between 12:00am and 3:00am should be counted as taken on the previous calendar date (i.e., the day before).

5. Adherence is calculated as taking all expected doses of medications, with each medication weighted equally.
    - E.g., If a patient has 1 QD med and 2 BID meds, their calculation would be (1/3)(X/1) + (1/3)(X/2) + (1/3)(X/2) = 1
6. Please provide the calculated daily adherence values for all the patients as a separate dataset containing the record_id and the calculated daily adherence values.
7. Separately, please also provide the daily adherence for Allopurinol QD only. This variable will later be used for sensitivity analysis. The daily adherence will be recorded as a binary variable (1/0) – (adh_daily_allopurinolqd)
    - E.g., if a patient takes 1 QD Allopurinol, their adherence for that day would be either 1 or 0.

c) Using these daily calculations, generate the following adherence measure outcomes:
1. Aggregate adherence (adh_daily) into the mean daily adherence value for each patient (ranging from 0 to 1) for the **18 weeks** from "start_date" to the end of follow up (if date range is less than 18 weeks, calculate just for the respective date range) → label this as "adherence_primary_outcome"
2. Repeat the aggregation of adherence for each patient omitting the first 7 days of data (i.e., index date -> index date+7)
3. Repeat the aggregation of adherence for each patient omitting the first 14 days of data (i.e., index date -> index date+14)
4. Repeat the aggregation of adherence for each patient, but censor patients in the adherence calculation at the time they have stopped using the electronic pill bottle for >30 days (defined as "adh_daily"=0 for >30 consecutive days in Pillsy data)
    - Please generate a flag for the patient (1/0) and provide the date in which they were censored if this occurs (leave the date as missing if does not occur)
5. Repeat the aggregation of adherence for each patient for the **12 weeks** from "start date" to the "intervention_date" (the intervention completion date) or "withdraw_date", whichever is earlier.
6. Repeat the aggregation of adherence (adh_daily_allopurinolqd) for 18 weeks from "start_date" to the end of follow up for Allopurinol QD – label as "adh _allopurinol".

d) Use generalized linear models (proc genmod) to compare nonadaptive vs. control and adaptive vs. control; calculate unadjusted mean differences for these groups and adjusted mean differences (adjusted for age, sex, race/ethnicity). The link=identity and dist=normal). Recruitment type (PCP vs. rheumatology) also accounted for in the model.

B) Uric acid level outcomes (Change in uric acid levels – Exploratory outcome)

a) Using the **REDCap file**:
- Please measure the difference between "ua_end" (outcome) and "ua_baseline" (baseline).
- Please provide the dates for both "ua_date_end" and "ua_baseline_date"
- Please provide a flag if missing "ua_end" (outcome)

b) Use generalized linear models (proc genmod) to compare nonadaptive vs. control and

adaptive vs. control; calculate unadjusted mean differences for these groups and adjusted mean differences (adjusted for age, sex, race/ethnicity). The link=identity and dist=normal). Recruitment type (PCP vs. rheumatology) and baseline uric acid level also accounted for in the model.

C) Self-Reported Outcomes:

- Automaticity scores (automaticity): automaticity_1_end to automaticity_4_end.
  - 0=No
  - 1=Yes
- Routine related questionnaire
  - Score the following from 1 to 7: routine_end, same_time_end, continue_way_end, take_same_place_end, take_right_before_end, take_water_end, take_same_cup_end, keep_same_place_end
- Perception related questionnaire
  - Score from 1 (Strongly Disagree) to 5 (Strongly Agree) the following: regular_apts_end, tx_plan_difference_end, med_help_control_end, prescribed_take_daily_end, not_taking_effect_end, feel_well_stop_end, live_long_end, control_gout_end, gout_better_worse_end, actions_effect_end

D) Feasibility Outcomes:

- Score from 1 (Strongly **agree**) to 5 (Strongly **disagree**) the following: cue_useful, cue_text_useful, reward_text_useful

Requested Results:

Table 1: Baseline characteristics

	Usual Care	**Non-adaptive**	**Adaptive**
N, (%)			
Age **(Mean, SD)** **(Median, IQR)**			
Female (N, %)			
Partnered/ Marital status Married Living with partner/ Domestic partnership Widowed Divorced/ Separated Never married/ Single			

Race White Black or African American American Indian/ Alaska Native Asian Native Hawaiian or Other Pacific Islander Hispanic/Latinx			
Education level Less than high school diploma High school diploma Some college College degree Graduate degree			
Employment Employed Job seeking Not job seeking Retired Disabled			
Baseline Uric acid (mg/dL)			
Medication Use Baseline Automaticity score (Mean, SD) Routine Perception			
Recruitment method Rheumatology (N, %) PCP (N, %)			
Self-reported medications on a daily basis (Mean, SD)			
Self-reported medications on a weekly basis (Mean, SD)			
Number of prescribed study medications (N, %) 1 2 3			
Baseline self-reported adherence (Mean, SD)			
Disease activity (Mean, SD)			
Number of Pillsy bottles used in the study			

1 2+			
Patients intensified (adaptive arm)			

Table 2: Primary and Secondary Outcomes

	Control Mean (SD)	Non-adaptive intervention Mean (SD)	Adaptive intervention Mean (SD)	Unadjusted absolute difference		Adjusted absolute difference	
				(Non-adaptive vs Control)	(Adaptive vs Control)	(Non-adaptive vs Control)	(Adaptive vs Control)
Primary Outcome:							
Adherence							
Secondary Outcome:							
Change in uric acid levels							
Change in automaticity							
Change in perception							
Change in sense of routine							