1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Regulatory Sponsor:
Global Coalition for Adaptive Research, Inc (GCAR)

Name of Funding Sponsor:
US Army Medical Materiel Development Activity (USAMMDA)

Name of Study Intervention:
Multiple interventions will be tested in this adaptive platform trial, and each will be described in intervention-specific cohort appendices to the master protocol

Name of Active Ingredient:
Active ingredients will be described in the cohort appendices.

Protocol Number:
S-21-02

Full Title of Study:
A Phase 2, Multi-center, Multi-arm, Randomized, Placebo-Controlled, Double-Blind, Adaptive Platform Trial to Evaluate the Safety, Tolerability, and Efficacy of Potential Therapeutic Interventions in Active-Duty Service Members and Veterans with Posttraumatic Stress Disorder (PTSD)

Study Short Title:
M-PACT (formerly DOD PTSD APT)

Study Sites: Approximately 20 sites in the US. A site list is maintained in the eTMF and updated as sites are added. The list is available upon request.

Studied Period (years):	**Phase of Development:**
First subject enrolled: Nov 2023 Estimated date last subject completed: Oct 2029	Phase 2

Duration of Subject Participation:
This study consists of a 30-day Screening Period, a 12-week Treatment Period, and a 4-week Safety Follow-up. The total duration of subject participation in this study is up to 20 weeks; if a subject is re-randomized, their total duration of participation will continue for an additional 16 to 20 weeks each time they are re-randomized.

Objectives:

Primary:

- Determine the efficacy and safety of each intervention for the treatment of PTSD in active-duty service members and veterans over 12 weeks.

Secondary:

- Evaluate the effect of each intervention on PTSD symptoms, sleep, depression, anxiety, substance use, functional status, mood, cognition, and QOL in active-duty service members and veterans with PTSD over 12 weeks.
- Identify PTSD subtypes through characterization of candidate biomarkers within the following categories:
  - diagnostic subtype biomarkers of population heterogeneity
  - predictive, monitoring biomarkers of treatment response for specific interventions
  - pharmacodynamic biomarkers of intervention effects

Exploratory:

- To explore the utility of physiological, biological, cognitive, and digital measures as diagnostic (eg, to identify PTSD subtypes), predictive, monitoring, and pharmacodynamic biomarkers in active-duty service members and veterans with PTSD for use in the design of biomarker extensions and intervention selection.
- To evaluate the effect of each intervention on each PTSD symptom and groups of PTSD symptoms (eg, cluster scores) in active-duty service members and veterans with PTSD over 12 weeks.
- To evaluate the effect of each intervention on the relationship between global impression of severity of PTSD and a change in PTSD symptom severity.
- To evaluate the effect of each intervention on subjects' most bothersome symptom.
- To evaluate the effect of each intervention on weekly PTSD symptoms, as measured by the PCL-5, Past Week.

Endpoints:

Primary:

Efficacy

- Absolute change from Baseline in CAPS-5-R, Past Month total score at Week 12 (Final/ET visit).

Safety

- Frequency and severity of TEAEs/SAEs.
- Absolute change from Baseline, and new clinically significant findings in clinical laboratory parameters, vital signs, physical examination, ECG.
- Incidence of new or worsening suicidal thoughts or behaviors as measured by C-SSRS.

Secondary:

- Relative change from Baseline to 12 weeks in CAPS-5-R, Past Month total score.

- Response rate: ≥30% reduction from Baseline to 12 Weeks in CAPS-5-R, Past Month total score.
- Response rate: ≥50% reduction from Baseline to 12 Weeks in CAPS-5-R, Past Month total score.
- Response rate: Achieving remission, defined as CAPS-5-R, Past Month total score <18.
- Relative and absolute change from Baseline in CAPS-5-R, Past Month total score at Weeks 4 and 8.
- Absolute change from Baseline at each post-Baseline visit in:
  - PCL-5, Past Week total score (at Weeks 4, 8, and 12)
  - PSQI-A
  - ISI
  - BDI-II
  - GAD-7
  - TLFB for substance use
  - FTND
  - B-IPF
  - WHOQOL-BREF
  - PSS
  - BPI
  - IDSIQ (mean average IDSIQ scores for 7-days prior to Weeks 4, 8, and 12)
- Diagnostic subtype: Analyses of biomarker levels across all interventions.
- Predictive: Relationship between baseline biomarker levels and absolute change from Baseline in CAPS-5-R, Past Month total score at Week 12 across all interventions or specific interventions.
- Monitoring: Relationship between a change in biomarker levels and absolute change from Baseline in CAPS-5-R, Past Month total score at Week 12 across all interventions or specific interventions.
- Pharmacodynamic: Relationship between a change in biomarker levels with administered doses of specific interventions through Week 12.

Exploratory:

- Modeling of individual or combinations of markers across all time points.
- Absolute change from Baseline to Week 12 in CAPS-5-R, Past Month severity scores on each PTSD symptom and groups of PTSD symptoms (eg, cluster scores).
- Absolute change from Baseline at each post-Baseline visit in:
  - CGI-S
  - PGI-S
  - PCL-5, Past Week

- Change from Baseline in the qualitative interview score at Week 12.

Trial Description:

The general structure of the M-PACT consists of a 30-day Screening Period, a 12-week Treatment Period, and a 4-week Safety Follow-up. The trial will include up to 5 open cohorts (it is possible for 1 of the cohorts to begin sooner than the others, as necessary). Importantly, the integration of multi-modal biomarker assessments within the M-PACT allows for defining future cohorts based on to-be-determined biomarker signatures in a multi-stage approach. Initial testing in non-biomarker-defined cohorts will be referred to as "main stage" testing, while testing in biomarker-defined cohorts will occur within "biomarker extensions."

In this study, cohorts will be allowed to enter and exit the overall adaptive platform trial, with exit based on a prescribed decision algorithm evaluating data as it accrues, and entry based on the PdM's decision informed by the DSWG and APEC's evaluation of potential new interventions for the trial. Thus, non-effective treatments may be identified more rapidly than in a traditional single intervention trial, and the resulting savings can be reinvested in exploring additional potential treatments.

Initially designed as up to 5-arms versus control, the adaptive platform trial will continue enrollment until decisions are made to stop all cohorts. At quarterly interim analyses, unblinded data will be reviewed by an independent, firewalled ISAC and a DSMB. At each interim analysis, the possible cohort-level decisions that could be made by the prespecified adaptive plan include stopping enrollment to a cohort for futility, stopping enrollment to a cohort for anticipated success, or stopping enrollment to a cohort for reaching the maximum sample size. For cohort-specific interventions intending to pursue a labeling claim (which will be clearly stated in the cohort-specific appendix before cohort initiation), early stopping for success will not be considered. New cohorts for investigation can be added at any time. The DSMB may recommend stopping any cohort for safety reasons.

Candidate biomarker data will be retrospectively analyzed after each cohort has completed main stage testing, and cohort testing may be re-initiated for prospective evaluation of the treatment in a subject population enriched (eg, either only biomarker "positive" or only biomarker "negative" subjects would be enrolled) or stratified based on biomarker status. In addition, candidate biomarkers (which may also be characterized or validated externally to the M-PACT) may be used to stratify randomization across cohorts or as a prospective enrichment strategy at the initiation of a cohort. Exploratory biomarker data will be evaluated throughout the trial to identify additional candidate biomarkers for testing within the M-PACT.

Study Description:

This is a Phase 2 randomized, double-blinded, placebo-controlled study that will evaluate multiple potential therapeutic interventions for PTSD utilizing an adaptive platform trial design. Subjects are randomized among the multiple cohorts in the study and the resulting randomization enables sharing/pooling of control subjects, where all interventions may be compared to a common control (placebo). This master protocol describes the default procedures and analyses for all cohorts; treatment-specific procedures will be described in the cohort appendices and individual cohorts may have additional eligibility requirements or safety and efficacy procedures.

Following Screening consent and Screening procedures, all eligible subjects who meet the protocol-defined criteria will be randomly assigned into 1 of the open cohorts for which the subject is eligible, with equal randomization among cohorts. Randomization will be stratified by gender, active military vs veteran status, and comorbid depression (yes/no). Following cohort-specific consenting, the subject will be randomly assigned (5:3; intervention:placebo) within the cohort to receive either intervention or placebo.

The Treatment Period will be 12 weeks, with efficacy, safety, and in-clinic biomarker assessments and procedures conducted at Weeks 1 and 12. Remote efficacy and safety measures will be conducted at Weeks 4 and 8. In addition, digital monitoring data will be collected remotely throughout the Treatment Period via smartphone and the Empatica EmbracePlus actigraphy device. Subjects will return at Week 16 (4 weeks after last dose of study intervention) for Safety Follow-up. Subjects who continue to meet inclusion/exclusion criteria for the study will be given the option to be re-randomized to an alternative cohort intervention or placebo for which they are eligible. Subjects can be re-randomized as often as they remain eligible for at least 1 cohort in the study and complete the appropriate washout period.

Number of Subjects:

The minimum sample size enrolled in each cohort is 64 subjects (40 subjects per active treatment and 24 subjects in each placebo arm). The maximum sample size enrolled in each cohort is up to 160 subjects (100 subjects per active treatment and 60 subjects in each placebo arm).

Diagnosis and Main Criteria for Inclusion:

- ≥18 and <65 years of age at Screening.
- Meets DSM-5 criteria for PTSD according to CAPS-5-R, Past Month assessment.
- Is at least 3 months post index trauma at Screening.
- Has a CAPS-5-R, Past Month total score of ≥26 at Screening. Note: the CAPS-5 scoring grid will be used to score answers and to calculate the total score to determine eligibility.
- Is currently serving, or has previously served, in a branch of the US military service (eg, Air Force, Army, Navy, Marine Corps, and Coast Guard including Reserves and National Guard).

Investigational Product

Multiple investigational products will be included in this trial. The dose, frequency, and method of delivery will vary depending upon the open cohort to which the subject is assigned.

Reference Therapy, Dosage, and Mode of Administration:

A placebo that matches the active treatment visually and in method and frequency of administration, but which contains no active ingredient, will be used for each study cohort.

Criteria for Evaluation

Safety/Pharmacovigilance:

- C-SSRS
- CSFQ
- Adverse events
- Concomitant medications
- Physical examination
- Vital signs (temperature, pulse, respiratory rate, and systolic and diastolic blood pressure)
- Clinical laboratory assessments (hematology, clinical chemistry, urinalysis, pregnancy test)
- 12-lead ECG

Efficacy/Effectiveness:

- CAPS-5-R, Past Month
- PCL-5, Past Week
- TLFB for substance use
- FTND
- PSQI-A
- IDSIQ
- BDI-II
- GAD-7
- B-IPF
- PSS
- BPI
- WHOQOL-BREF

Biomarker Collections:

- MRI
- Biological samples (blood and hair)
- Psychophysiological testing
- Cognitive battery
- Actigraphy device (Empatica EmbracePlus)

Statistical Methods:

Primary Estimand: The primary estimand is the difference between treatments (intervention - placebo) in mean absolute change from Baseline (final CAPS-5-R, Past Month total score - Baseline CAPS-5-R, Past Month total score) in final total score at Week 12 (Final/ET visit) during the Treatment Period in active-duty service members and veterans with PTSD, regardless of treatment adherence, treatment change and discontinuation of study intervention for reasons related to study intervention (lack of efficacy/tolerability) or logistical, and use of prohibited medications, and that death would constitute treatment failure, ie, a composite strategy.

Interim analyses will be conducted quarterly. At each interim analysis, the unblinded data will be reviewed by an independent, firewalled ISAC that will produce a report detailing the current status of each cohort. At each interim analysis the following decisions can be made:

1. Stop enrollment to a cohort for futility.
2. Stop enrollment to a cohort for anticipated success (unless the data will be used to support a labeling claim).
3. Stop enrollment to a cohort for reaching the maximum sample size. This may happen between interim analyses, at which point the cohort will be stopped immediately.
4. Add new cohorts to the trial (this may occur at any time). These additional cohorts could be interventions to be investigated in the main stage or interventions that have completed the main stage and are being investigated additionally in a biomarker extension.

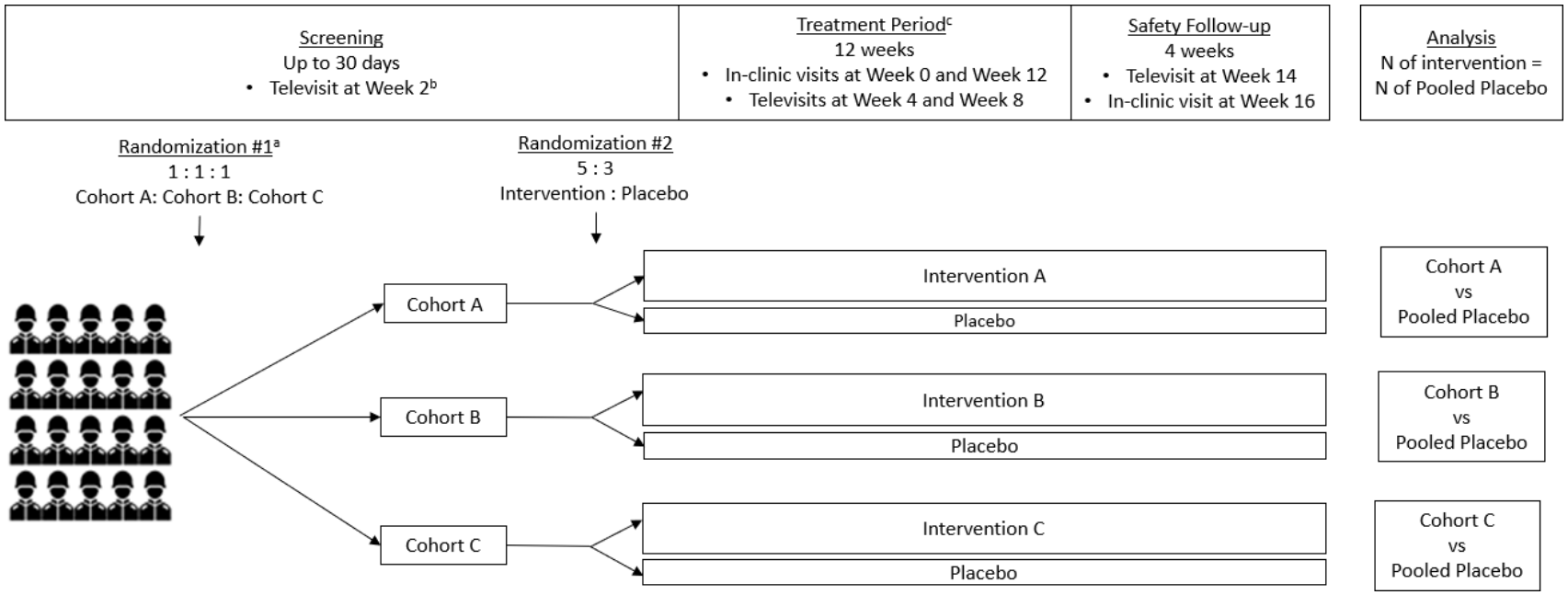
Success stopping (for cohort-specific interventions not pursuing labeling claims) will be driven by the predictive probability of success at current N. At any interim analysis, complete data will be available on some subjects (those enrolled at least 12 weeks prior to the interim) and incomplete data on others (those enrolled in the 12 weeks prior to the interim). To allow for a successful flexible sample size design, a "Goldilocks" strategy will be employed where the probability of success is predicted, with the assumption that upon receipt of endpoint data from incomplete subjects, the final success criteria will be met (Broglio et al 2014). If this probability is high, the cohort may cease enrollment for "anticipated success." Follow-up of all subjects will be conducted to their final endpoint and the final analysis will then be conducted. A cohort will cease enrollment for anticipated success if the predictive probability of success is greater than 90%.

Futility stopping will be governed by the predictive probability of success at the maximum sample size, N. The predictive probability that the final efficacy criteria will be met if the cohort goes forward to the maximum sample size will be computed. If this probability is small, it indicates that even with full enrollment to a cohort, the cohort is unlikely to ultimately be successful. A cohort will stop for futility if the predictive probability is less than 10%.

The DSMB may recommend stopping any cohort for safety reasons.

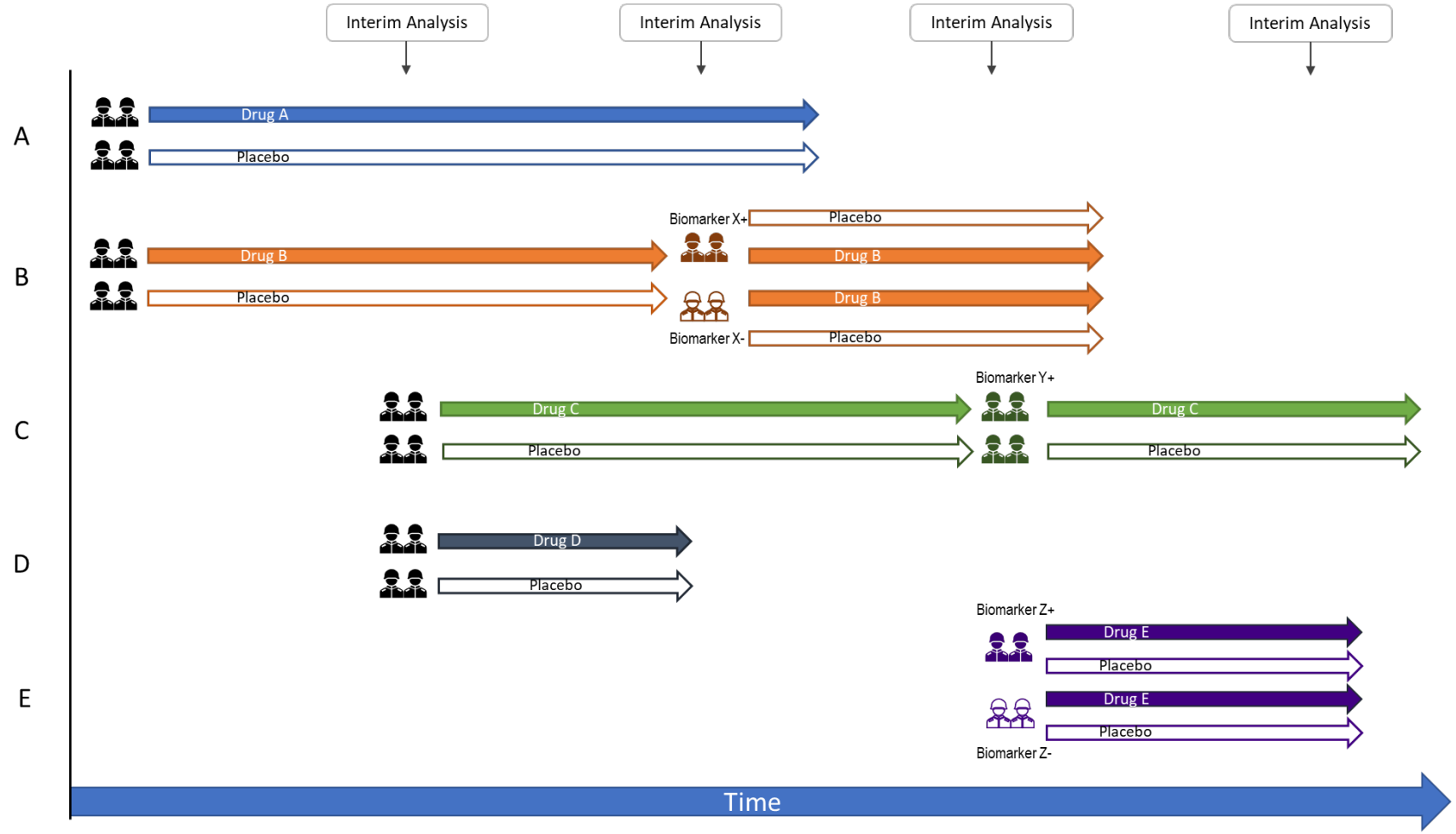
1.2. Schema

Figure 1: Schematic of the Trial Design



a. Up to 5 cohorts may be active for randomization.
b. Applicable for subjects undergoing washout for applicable medication.
c. Subjects who continue to meet inclusion/exclusion criteria for the study will be given the option to be re-randomized to another cohort intervention or cohort placebo for which they are eligible. Subjects can be re-randomized as often as they remain eligible for at least 1 cohort in the study and complete the appropriate washout period. See Table 2 and Section 5.4.1 for more details on re-randomization.

Figure 2: Schematic of a Hypothetical Platform Study Design with Continuous Learning and Biomarker Development



The M-PACT is a perpetual trial where cohorts can be added, removed, or extended based on accumulating trial data. Biomarker classification used to categorize the sensitivity of treatment response is unknown at the start of the trial, represented by black figures. Subjects have equal probability of randomization to any cohort for which they are eligible. They are then randomized 5:3 between study intervention and placebo (see Figure 1). Candidate biomarkers, which may be common to the trial or specific to a cohort, are tracked along with the primary endpoint to identify potential predictors of, or biomarkers associated with, treatment response. Possible outcomes for cohorts are shown above. **A. Cohort graduation:** Cohort reaches maximum sample size. Drug A is superior to placebo in all subjects. **B. Biomarker extension:** Validation. After the main stage of the cohort (target sample size reached or futility or success threshold met),

Drug B is not superior to placebo in all subjects. Candidate Biomarker X is identified as possibly predictive of treatment response. Validation extension establishes that a drug's treatment effect differs over the range of the biomarker (X+ (dark orange) and X- (white) subgroups). **C. Biomarker extension:** Enrichment. Drug C is not superior to placebo in all subjects. Candidate Biomarker Y identifies a treatment sensitive subgroup. Enrichment extension determines if Drug C is superior to placebo in the Y+ (dark green) subgroup. **D. Cohort is dropped for futility:** Future probability of success crosses the futility boundary at an interim analysis. **E. Diagnostic subtype biomarker:** Ongoing data collection and analysis of data from all cohorts, or within a cohort, identifies a Biomarker Z as sufficiently promising to be tested as a diagnostic subtyping biomarker for new Drug E with a mechanism of action related to Biomarker Z, or in a treatment that has already completed the main stage of the platform. Biomarker Z could also be identified externally to the trial and be sufficiently validated to bypass the learning stage of the platform.

Figure 3: Randomization and Re-randomization Flow Chart