RATIONAL AND AIMS OF A PHASE 2, MULTI-CENTER, MULTI-ARM, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, ADAPTIVE PLATFORM STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF POTENTIAL THERAPEUTIC INTERVENTIONS IN ACTIVE-DUTY SERVICE MEMBERS AND VETERANS WITH POSTTRAUMATIC STRESS DISORDER (PTSD)

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Disclaimer and Disclosure

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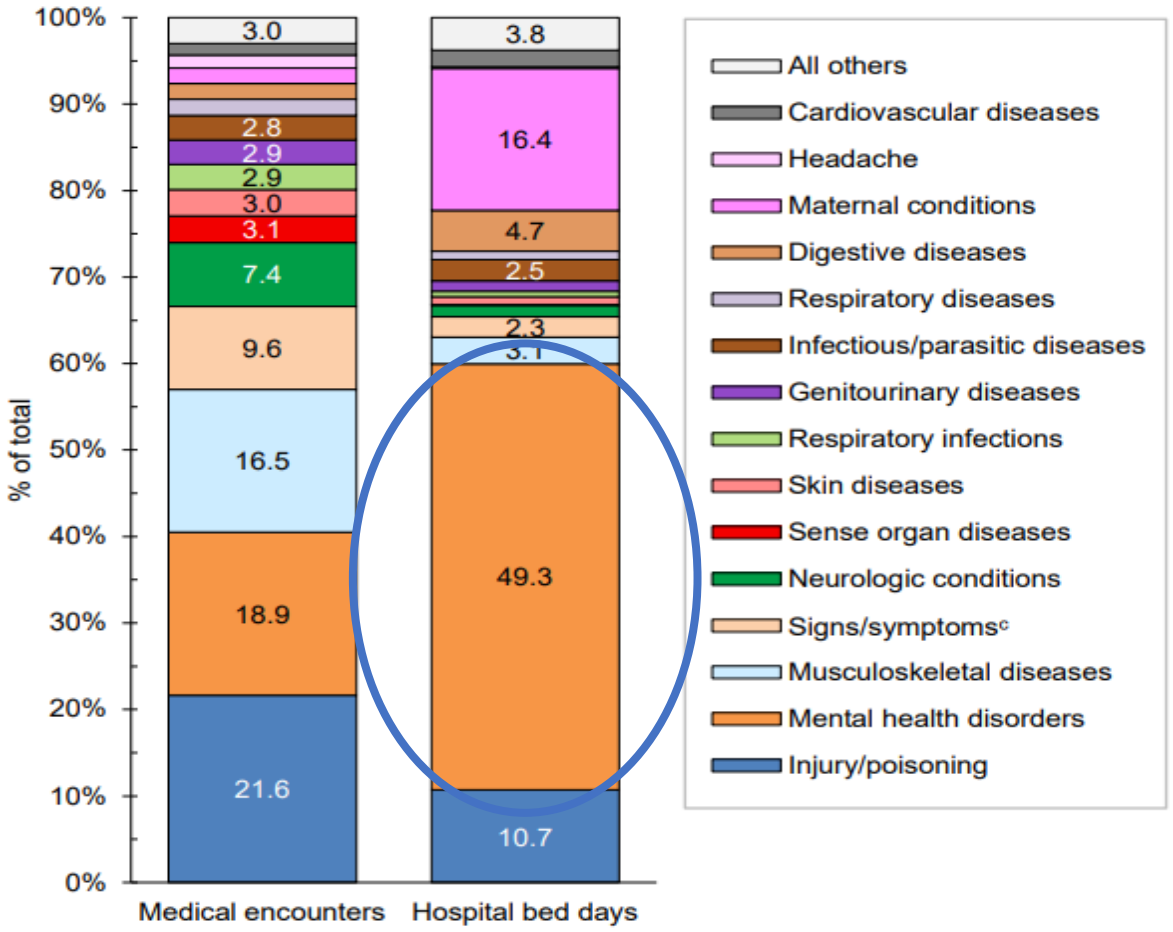
Disclosure: Owner of Pfizer, Inc. stock

The Impact of Mental Health Disorders on DOD Medical Readiness

FIGURE 1b. Percentage of medical encounters[a] and hospital bed days, attributable to burden of disease major categories,[b] active component, U.S. Armed Forces, 2020



Readiness Impact

In 2020, mental health disorders accounted for:

- **More hospital bed days** (n=165,296) than any other morbidity category
- **Half** of all hospital days overall (49.3%)

Mental health disorders were the **most common cause** of medical evacuation (n=328; 27.2%)[1]

[1] Armed Forces Health Surveillance Center Medical Surveillance Monthly Report. May 2021

PTSD Treatment Effect in Military Samples

- Treatment of PTSD remains an unmet need for civilians and military, however pharmacotherapeutic treatment efficacy for active-duty service members and veterans is lower or unknown.
  - Friedman et al 2007[1]
    - Sertraline did not perform better than placebo in military veterans (p=.26)
      - CAPS-2 point change from baseline:
        - Sertraline: -13.1 (3.0)
        - Placebo: -15.4 (3.1)
  - Katz et al (in preparation)[2]
    - Change in CAPS in military sample (35 studies, 2154 subjects) = -18.22 points
    - Change in CAPS in civilian sample (36 studies, 1153 Subjects) = -37.01 points
      - R^2=56.7%, P<0001

[1]Friedman MJ, Marmar CR, Baker DG, Sikes CR, Farfel GM. Randomized, double-blind comparison of sertraline and placebo for posttraumatic stress disorder in a Department of Veterans Affairs setting. J Clin Psychiatry. 2007;68(5):711-720.
[2]Katz, E., Brown, M., Kan-Dobrosky, N., Lyons-Zincyn, H., Hoffman, E., Rasmusson, A. Predictors of treatment and placebo response across PTSD drug trials: A meta-analysis and meta-regression. In Preparation.

DOD PTSD-Drug Treatment Program Requirement and APT Goals

- **Background:** Funded by the Defense Health Agency. Managed by the Warfighter Brain Health Project Management Office at the US Army Medical Material Development Activity.

- **Requirement:** To develop drugs that effectively treat PTSD to ensure service members are deployable and allow them to return to and/or remain in the fight.

- **Approach:** Utilize an **Adaptive Platform Trial (APT)** design to achieve the following:
  1. Efficiently test multiple drugs for the treatment of PTSD in a military cohort (active duty and veteran) within a common infrastructure
  2. Collect “deep” clinical and multimodal biological data to inform treatment selection, treatment response, and target engagement
  3. Validate biomarkers within the clinical trial infrastructure
  4. Perform testing under a Master Protocol IND to support FDA approval/clearance
  5. Partner with industry, other government agencies, and academia for testing and validation of drug treatments and biomarkers

DOD PTSD APT: Objectives

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

Secondary Objectives:

1. Evaluate the effect of each intervention on PTSD symptoms, sleep, depression, anxiety, substance use, functional status, and quality of life in active-duty service members and veterans with PTSD over 12 weeks.
2. Identify PTSD subtypes through characterization of candidate biomarkers within the following categories[1]:
   - Diagnostic subtype biomarkers of population heterogeneity
     - APT treatment selection
     - Target ID/validation
   - Predictive biomarkers of treatment response for specific interventions
     - Clinical treatment selection
   - Monitoring biomarkers of treatment response for specific interventions
     - Surrogate endpoints of efficacy
   - Pharmacodynamic biomarkers of intervention effect
     - Target engagement
     - Dose-response characteristics

[1]FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016-. FDA-NIH Biomarker Working Group. 2016 Jan 28 [Updated 2021 Jan 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK338449/ Co-published by National Institutes of Health (US), Bethesda (MD).

DOD PTSD APT: Key Study Parameters

Sample Size:

- Flexible sample size: 40 to 100 per cohort (completers), based on quarterly interim analyses for “success” or “futility”

Key Inclusion Criteria:

- Active Duty or Veteran
- CAPS-5-R score of ≥26

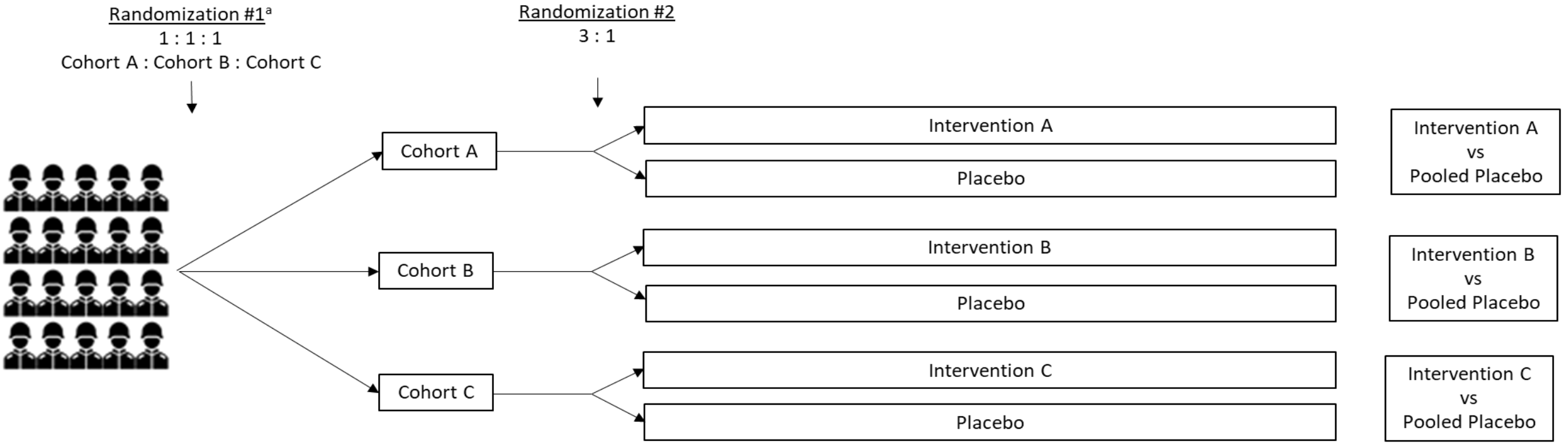
Key Exclusion Criteria:

- Prohibited/psychotropic medication
- Suicidality, Moderate or Severe AUD/SUD, Psychosis
- Obstructive Sleep Apnea, not well-managed by C-, Bi-, or V-PAP (AHI>5)
- Recent (last 3 months) or imminent changes in psychotherapy

[1]FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016-. FDA-NIH Biomarker Working Group. 2016 Jan 28 [Updated 2021 Jan 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK338449/ Co-published by National Institutes of Health (US), Bethesda (MD).

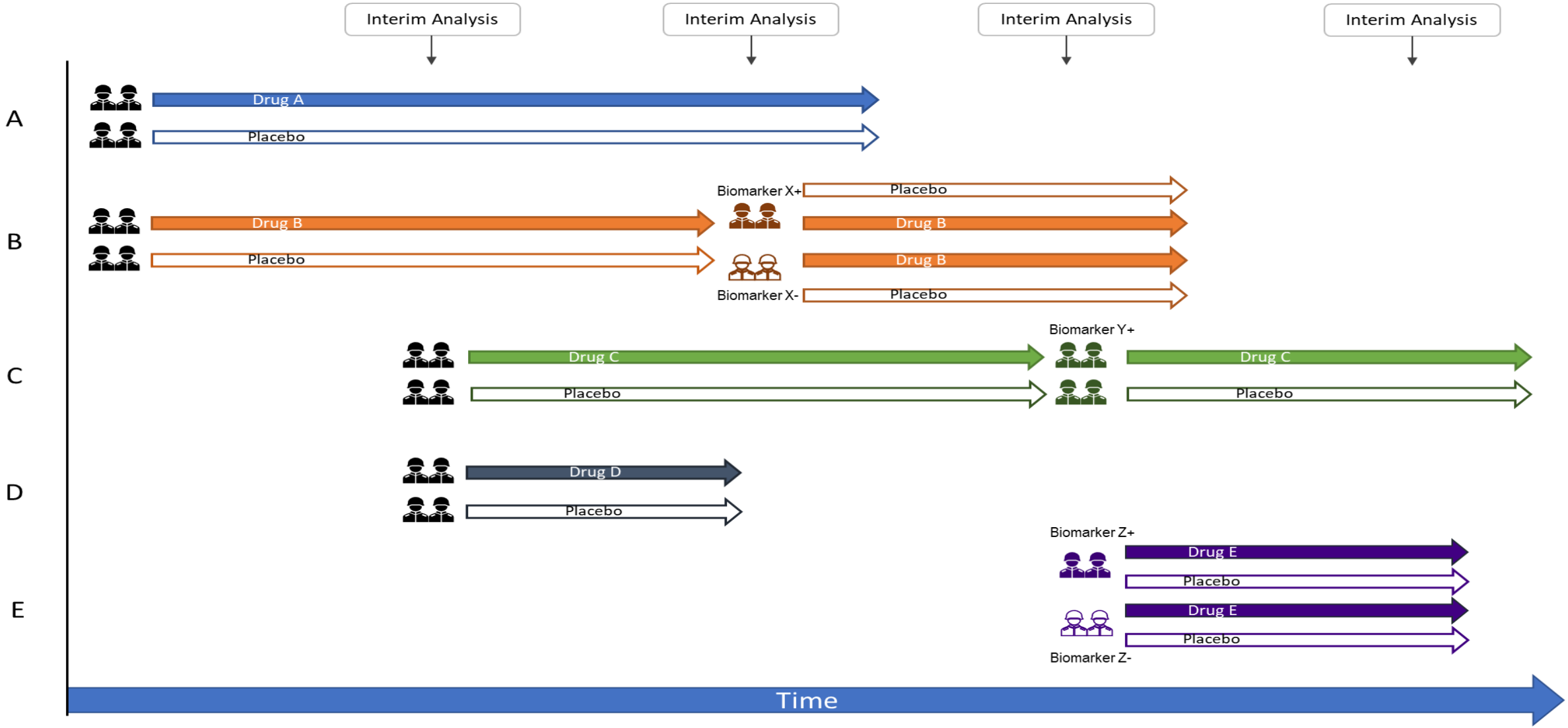
Adaptive Platform Trial Schematic

Screening	Platform Treatment Period[c]	Safety Follow-up	Analysis
Up to 30 days • Televisit at Week 2[b]	12 weeks • In-clinic visits at Week 0 and Week 12 • Televisits at Week 4 and Week 8	4 weeks • Televisit at Week 14 • In-clinic visit at Week 16	N of intervention = N of Pooled Placebo



[a] More or less than 3 cohorts may be active for randomization.
[b] As applicable for subjects undergoing washout for applicable medication.
[c] Subjects who have CAPS-5-R, Past Month total score ≥26 at Week 12 and 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 arm in the study.

DOD PTSD APT: Theoretical Framework for Continuous Learning and Biomarker Development



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  - Drug Selection Working Group
  - Clinical Working Group
  - Biomarker Working Group
- PPD, Inc.
- Berry Consultants, LLC
- Informa Business Intelligence, Inc.