

MEMANTINE AND EXERCISE FOR CANCER-RELATED COGNITIVE IMPAIRMENT DURING CHEMOTHERAPY FOR BREAST CANCER

STUDY PROTOCOL AND PRELIMINARY RESULTS

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BACKGROUND

- Up to 75% of patients with breast cancer report cognitive decline during chemotherapy
- Cancer-related cognitive impairment (CRCI) can have profound consequences on occupational, mental health, and other quality of life outcomes
- There is a clear need for mechanistically-based treatments [1]

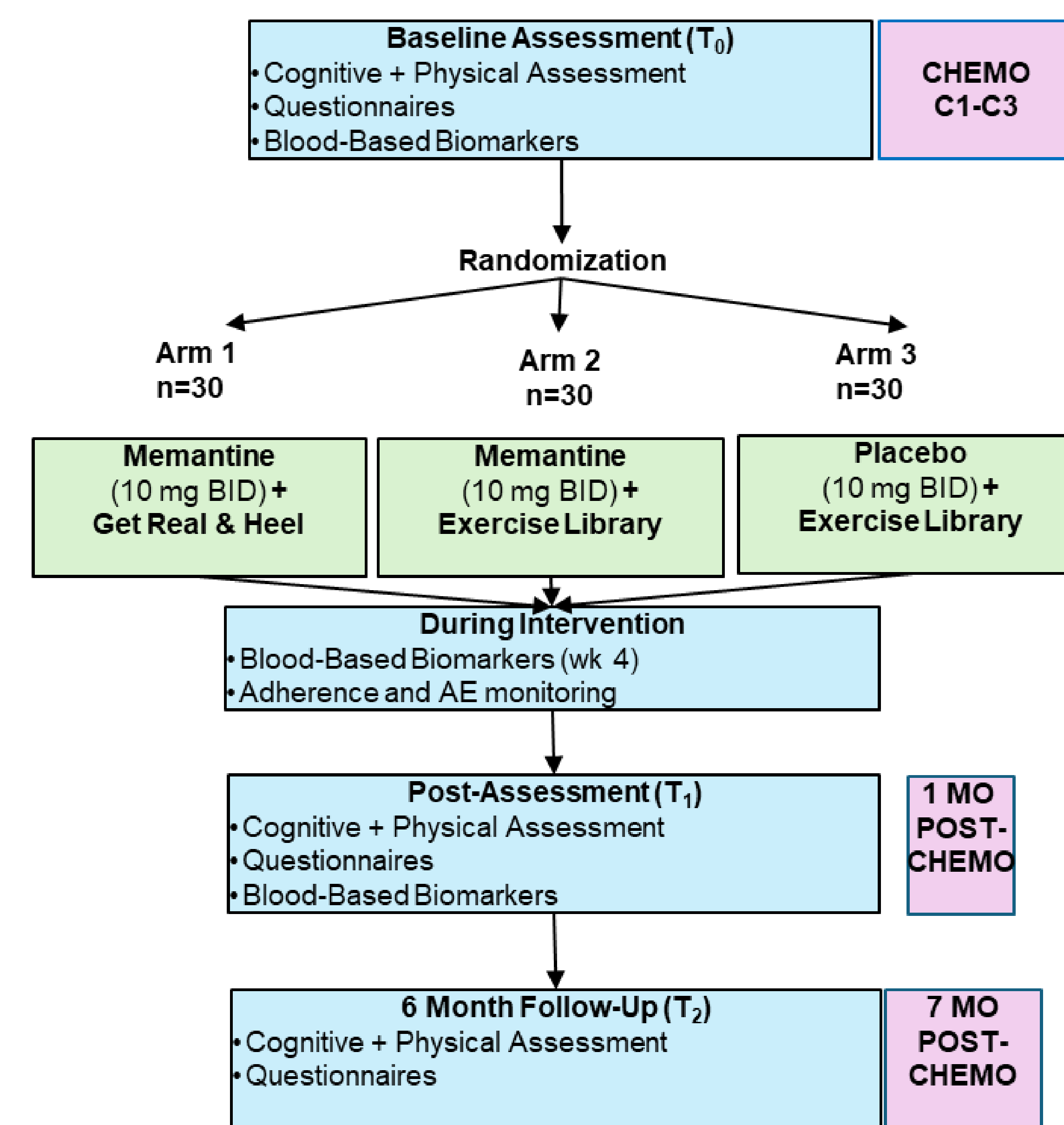
METHODOLOGICAL ISSUES BEING ADDRESSED

- Multicomponent, mechanistically-focused intervention in a complex clinical context
 - CRCI candidate mechanisms include neuroinflammation and neurotrophin depletion
 - Prior CRCI trials have been monotherapeutic, untargeted with limited benefit
- Multimodal cognitive profiling
 - Neuropsychological assessment
 - Computerized cognitive neuroscience
 - Patient self-report
- Data reduction technique
 - Gatekeeper approach [2]
 - Composite domain indices for cognitive and biomarker outcomes
 - Minimize type 1 error
 - Enhance power

AIMS

- Feasibility and acceptability
- Preliminary efficacy for CRCI
- Preliminary efficacy for CRCI biomarkers
- Exploratory: Frailty as a treatment modifier

METHODS



OVERVIEW

- Stage I-III breast cancer, scheduled or beginning to receive (within first 3 cycles) chemotherapy (n=90)
- Randomized 1:1:1 to memantine + exercise, memantine, or placebo
- Timepoints: Baseline, 1 mo*, 7 mo post-chemotherapy
 - *primary endpoint

DESIGN ADVANTAGES & DISADVANTAGES

- Efficient for conditions with heterogeneous mechanisms and phenotypes
- Multiple intervention components complicate interpretation
- Composite outcome measures
 - Reduce influence of isolated positive findings
 - Improve sensitivity to domain-level effects
 - Less translatable to clinical practice

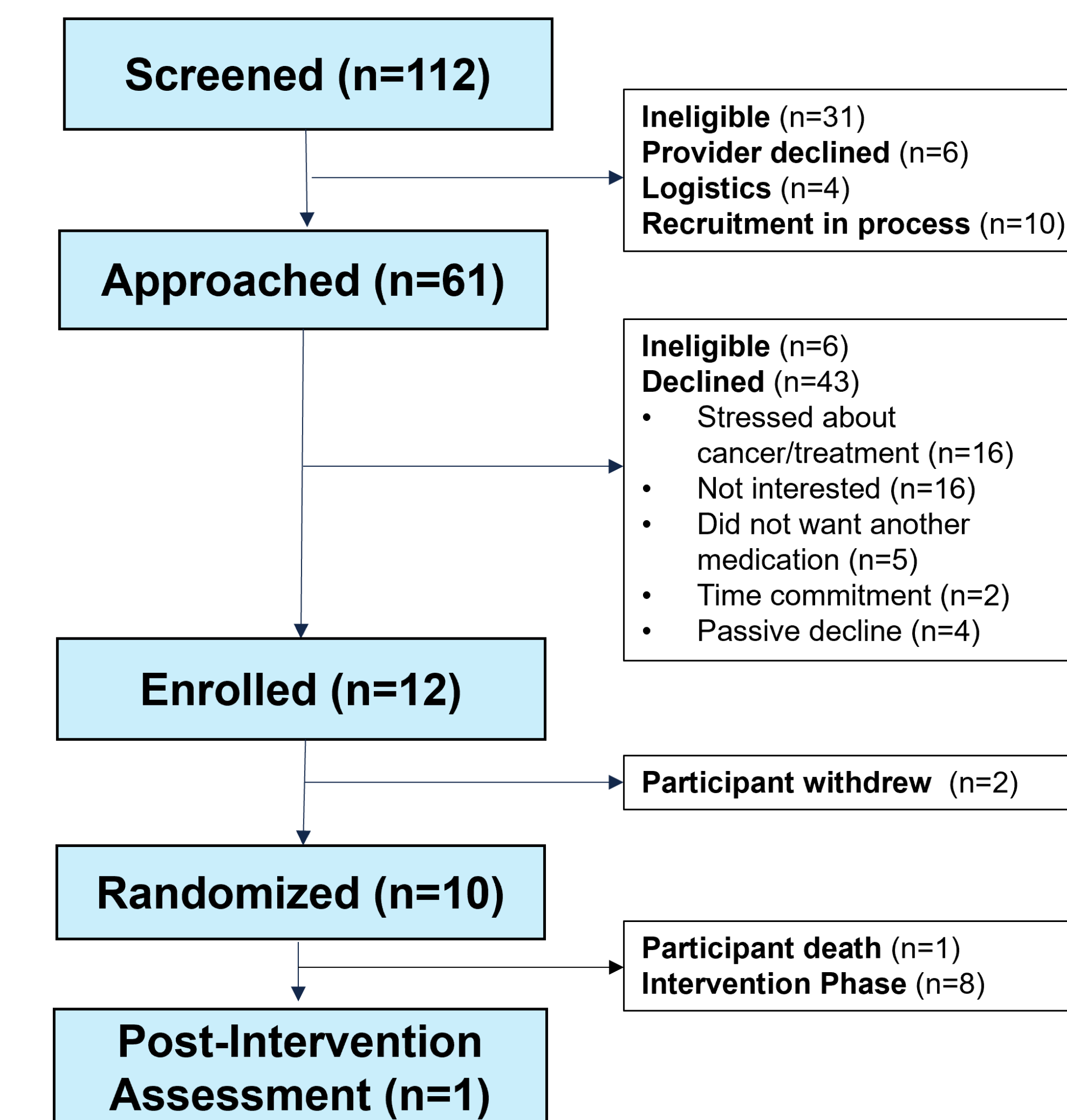
OUTCOME MEASURES

- Feasibility:** Recruitment, Retention, Adherence
- Acceptability:** Client Satisfaction Questionnaire
- Attention/Executive Function*:** Digits Forward & Backwards, Trails A & B, Animal Naming, COWA
- Learning/Memory*:** HVLT-R, BVMT-R
- Self-Report*:** Functional Assessment of Cancer Therapy – Cognitive Function (FACT-Cog PCI)
- CANTAB:** Delayed Matching to Sample, One Touch Stockings, Stop Signal Task
- Blood-based biomarkers:** BDNF and inflammatory composite[†] (CRP, TNF- α , IL-6)
- Physical activity/function:** actigraphy, 6-minute walk test, short physical performance battery
 - *primary efficacy outcomes; [†]sum of z-scores of individual substests

PRELIMINARY RESULTS

CHARACTERISTICS	N=12
	% (N)
Age, mean (SD)	57.3 (13.8)
Race	
White	50 (6)
Black or African-American	33 (4)
Other	17 (2)
Education, mean (SD)	16.7 (2.1)
WTAR FSIQ, mean (SD)	109.2 (12.0)
Stage	
I	50 (6)
II	17 (2)
III	33 (4)
HER2+	25 (3)
HR+	58 (7)
Surgery	50 (6)
Chemotherapy Regimen	
AC-T	25 (3)
AC-TC	8 (1)
TC (+/- HER2)	42 (5)
Other	25 (3)
FACT Cog PCI (0-72, higher better)	
Mean (SD)	57.1 (12.1)
\geq Mild impairment (≤ 54)	36 (4)

BASELINE COGNITIVE FUNCTION	T-score, mean (SD)
Attention/Executive Function Composite	51.9 (8.7)
Digits Forwards	46.7 (9.0)
Digits Backwards	47.0 (11.9)
Trails A	56.3 (21.9)
Trails B	51.6 (18.5)
Animal Naming	58.4 (11.6)
COWA	51.3 (10.8)
Learning/Memory Composite	52.3 (7.7)
HVLT-R Total Recall	51.0 (11.4)
HVLT-R Delayed Recall	47.3 (13.0)
BVMT-R Total Recall	54.1 (9.4)
BVMT-R Delayed Recall	56.6 (9.2)



FEASIBILITY

- Opened May 2025; first enrolled August 2025
- | | To date | Target |
|--|----------|----------|
| Recruitment | | |
| # Enrolled (per month) | 12 (2.4) | 90 (2.5) |
| enrolled/approached | 22% | 40% |
| Retention (completed & active/enrolled) | 75% | 85% |
| Medication adherence (doses taken/scheduled) | 90% | 90% |
| Exercise adherence (classes attended/scheduled) | 76% | 75% |
- Among n=12, 2 AEs attributed to intervention: myalgia (Gr 1), constipation (Gr 2)

CONCLUSIONS

- Recruitment on pace to reach n=90
- Rate of refusal higher than anticipated; stress about cancer/treatment is most common reason
- Retention and adherence comparable with targets
- Few intervention-related AEs
- At pre-chemotherapy baseline
 - 36% report \geq mild cognitive impairment
 - None >1.5 SD below population norms on AE and LM domains
- Multicomponent intervention with multimodal cognitive profiling and gatekeeper-based analytic approach addresses key methodological challenges in CRCI trials
- Scalable model to test complex interventions with multidomain outcomes and limited sample size

REFERENCES

- Schagen SB, Tsvetkov AS, Compter A, Wefel JS. Cognitive adverse effects of chemotherapy and immunotherapy: are interventions within reach? *Nat Rev Neurol.* 2022 Mar;18(3):173–85.
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