



Feasibility of a phase 1 clinical trial of a *Centella asiatica* product in older adults with mild cognitive impairment

Kirsten M. Wright¹, Alex Speers¹, Jesus Martinez¹, Manoj Sammi², Madeline Waldram¹, Melissa Bollen¹, Deanna Gold¹, Samantha Varada¹, Cody Neff¹, Noah Gladen-Kolarsky¹, Morgan Wilhelmi¹, Taryn Machingo¹, Tatevik Mazmnyan¹, Katlin Wozniak¹, Mac Day¹, Seiji Koike³, Thuan Nguyen³, Nora Gray¹, Joseph Quinn^{1,4}, Amala Soumyanath¹

¹ Department of Neurology, Oregon Health & Science University, Portland, OR, USA, ² Advanced Imaging Research Center, Oregon Health & Science University, Portland, OR, USA, ³ Biostatistics and Design Program, Oregon Health & Science University, Portland, OR, USA, ⁴ Department of Neurology, Portland Department of Veterans Affairs, Portland, OR, USA

INTRODUCTION

- Centella asiatica* (CA) is an Ayurvedic botanical reputed to improve memory.¹
- CA is sold as the dietary supplement “gotu kola” to improve brain health and cognitive function.²
- Preclinical studies of a CA water extract (CAW) have shown biological effects of relevance to memory,^{3,4} learning, aging, mood⁵⁻⁷ and disease progression in Alzheimer’s disease (AD), including increased expression of Nrf2 and antioxidant response element genes,⁸ mitochondrial electron transport chain genes and synaptic genes, modulation of oxidative stress,⁹ and stimulation of mitochondrial activity and neuronal dendritic arborization.¹⁰⁻¹² These effects were not consistently accompanied by a change in brain amyloid beta (A β) *in vivo*.¹³
- Human trials of a standardized oral CAW product (CAP) in older adults have demonstrated bioavailability of known CA bioactives and tolerability of acute dosing.^{14,15}



OBJECTIVE

Establish feasibility of chronic CAP dosing, product safety, and measurement of biological markers of target engagement in older adults with mild cognitive impairment (MCI) prior to a Phase 2 efficacy trial.

METHODS

- Randomized, double-blind, single-dose, placebo-controlled Phase I clinical trial (n=48; NCT05591027)
- Recruitment from the Portland, Oregon, USA metropolitan area from August 2022 to July 2025
- Randomized to 4g CAP or matching placebo consumed orally as a powder mixed in water once daily (morning) for 6 weeks
- Outcome measures (baseline and 6 weeks):
 - Safety and tolerability
 - Safety laboratory assessments, electrocardiogram
 - 2, 4, 10, 12-week phone adverse event assessments
 - Brain neuronal viability and bioenergetics via brain ¹H-magnetic resonance spectral imaging (MRSI) and ³¹P-MRSI
 - Peripheral oxidative stress, Nrf2 activation, mitochondrial activity, and biomarkers of neurodegeneration in blood (NfL, GFAP, A β 40, A β 42, A β 40/42, p-tau 217)

Inclusion criteria:

- Older adults (age 60-85 years) diagnosed with MCI or mild AD
- Mini Mental Status Exam score = 18 – 28, inclusive
- Global Clinical Dementia Rating score = 0.5 – 1, inclusive
- Geriatric Depression Scale-15 score = < 5
- Body mass index (BMI) = 17 - 35
- Stable acetylcholinesterase inhibitor or memantine use for 12 weeks and no active use of anti-amyloid immunotherapy
- Study partner to accompany to visits

Exclusion criteria:

- Current smoking, alcohol, or substance abuse (DSM-V Criteria)
- Abnormal baseline safety labs (CBC, CMP, urinalysis, electrocardiogram)
- Cancer within five years, except for localized prostate cancer and non-metastatic skin cancers
- Poorly controlled type II diabetes mellitus, kidney failure, liver failure, blood disorders, or unstable or significantly symptomatic cardiovascular disease
- Significant disease of the central nervous system (i.e., brain tumor, seizure disorder, subdural hematoma, cranial arteritis, or clinically significant stroke)
- Non-Alzheimer’s disease dementia (i.e., vascular dementia, normal pressure hydrocephalus, or Parkinson’s disease)
- Contraindications to MRSI (metal implants, claustrophobia)

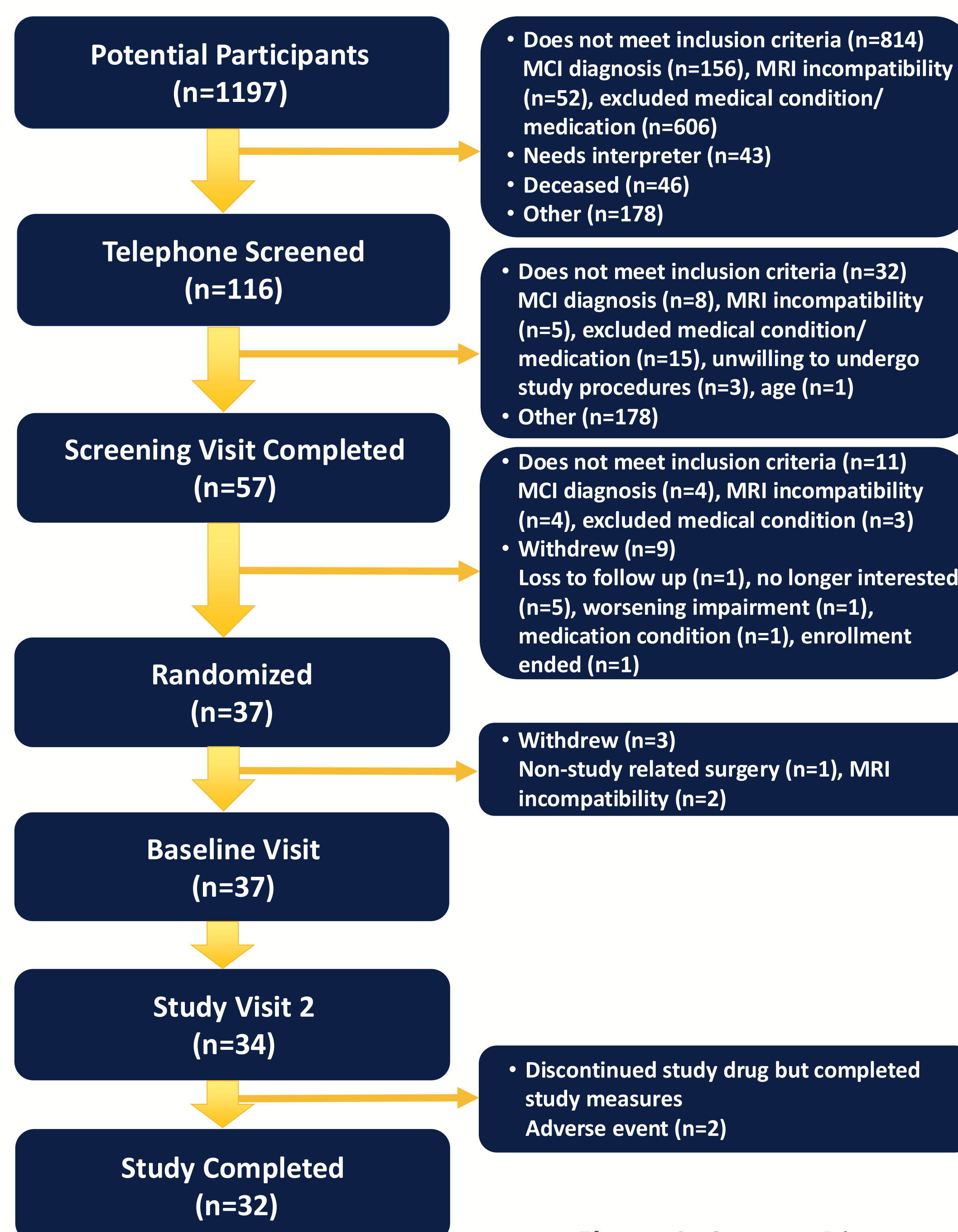


Figure 1. Consort Diagram

RESULTS

- 57** participants were **screened** in-person, 65% were randomized.
- 37** older adults were **randomized** (mean age = 74.6 $\pm$ 4.4 years, 46% female, 5.6% from underrepresented groups; 77% of target).
- 32** participants **completed** all intervention and outcome measures* (86%) with no difference in study dropout rate between intervention groups (p=0.66). *4 did not complete ³¹P MRSI.
- Study intervention was well tolerated with high adherence (96%) and no significant differences between baseline and 6 weeks in clinical safety assessments within treatment group (p= 0.08-0.95) or total adverse events between CAP and placebo (p=0.18-1.00), including frequency (p=0.15-0.97) and severity (p=0.10-0.92).

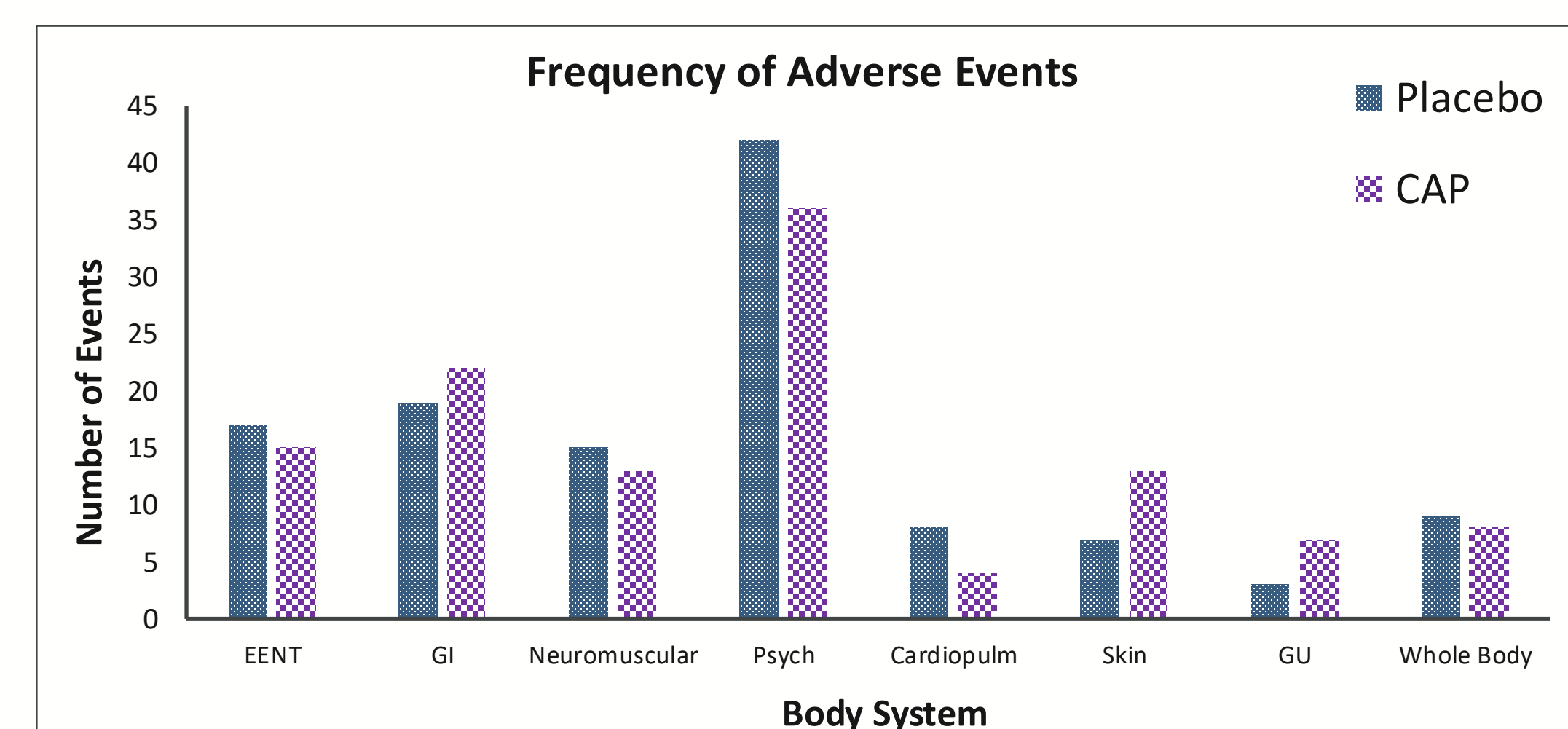


Figure 2. Total number of adverse events by body system. EENT = Eyes, Ears, Nose, Throat; GI = Gastrointestinal; Psych = Psychological; Cardiopulm = Cardiopulmonary; GU = Genitourinary

CONCLUSIONS

- Older adults with MCI or mild AD can be recruited into and complete a six-week Phase 1 clinical trial of a standardized, oral CAP drink intervention with low dropout (13.5%).
- Chronic CAP dosing is safe and well-tolerated in cognitively impaired older adults at 4g CAW dose/daily.
- MRSI outcome measures are a barrier to enrollment of older adults due to frequency of metal implants and use of stronger magnets (3 and 7 Tesla) for research outcomes.

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