



A Prospective, Double blind, Randomized, Sham-Controlled, Clinical Trial to Evaluate the Safety and Efficacy of Biometrics-guided Magnetic EEG Resonance Therapy (MeRTSM) treatment of Persistent Post-Concussive Symptoms (PPCS) following Traumatic Brain Injury (TBI)

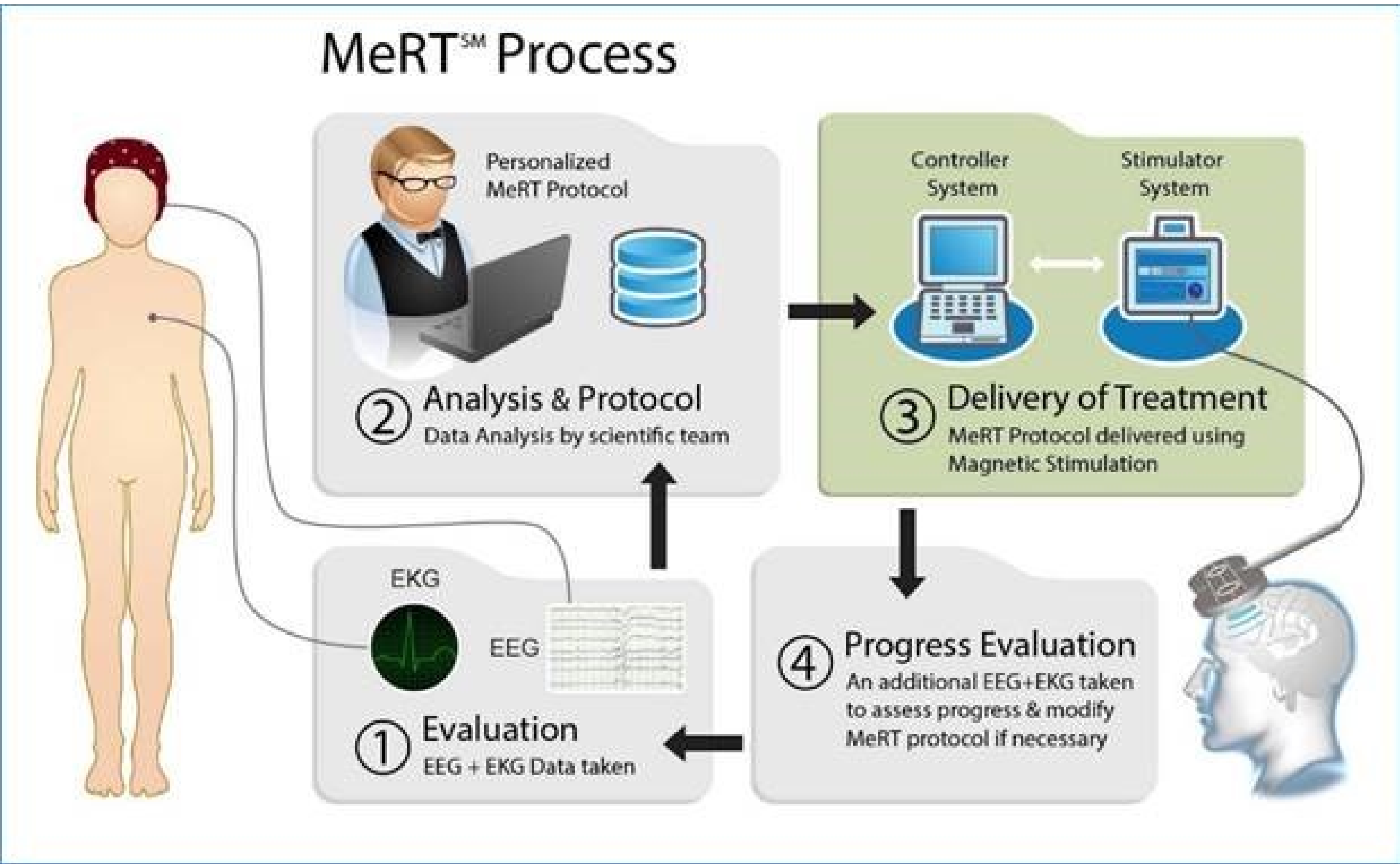
Gilpin A^{1,7}, Cellucci C², Chung J³, Cota S⁴, Darmon D⁵, Keyser D⁶, Phillips W¹, Rapp P⁶, Trongnetrpunya A⁶, Wang C⁶, and Won E¹

¹ Wave Neuroscience dba Newport Brain Research Laboratory, Newport Beach, CA; ² Aquinas LLC, Berwyn, PA; ³ USN Camp Pendleton, CA; ⁴ USN Camp LeJeune, NC; ⁵ Monmouth University, West Long Branch, NJ; ⁶ Uniformed Services University, Traumatic Injury Research Program, Bethesda, MD; ⁷ Gilpin BIOMED, PLLC, Silver Spring, MD

Introduction:
This is a multicenter (4 clinical sites, Coordinating Center, Data Coordinating Center, Electrophysiology Resource Center, and Data and Safety Monitoring Board) double blind, sham-controlled, parallel group, randomized clinical trial, with adaptive features. Adaptive features intended to assure that study-wide statistical power remains at the design value of 82% include a blinded sample size reassessment option, and blinded monitoring of the Rivermead Post-concussion Questionnaire (RPQ) eligibility criterion.

The study evaluates individualized, Biometrics-Guided Magnetic EEG Resonance Therapy (MeRTSM) treatment of Persistent Post-Concussive Symptoms (PPCS) following Traumatic Brain Injury (TBI). Target enrollment is 150 active duty, reservist on active duty orders, National Guard on active duty orders, veterans, or military retiree, U.S. military service persons with PPCS following TBI are being enrolled. Participants are evaluated for eligibility at the Screening Visit (SC), and Baseline (BL) Visit. Eligible Participants are randomly assigned to active MeRT or Sham MeRT study treatment groups in a 1:1 allocation ratio, with randomization stratified by site and by military status (active duty/retiree). There are 20 treatment visits (T1 – T20), limited to 1 per day, to be completed in a maximum of 35 study (calendar) days. Two follow-up data collection visits are conducted, in which follow-up visit 1 (F1) is conducted approximately half-way through the treatment protocol, and follow-up visit 2 (F2) is conducted after the last treatment has occurred, and no later than study day 48.

Participant Characterization:
Alcohol Use Disorders Identification Test, Brief Resilience Scale, Combat Exposure Scale , Columbia Suicide Severity Rating Scale, Demographics/Military Information Form, Defense and Veterans Pain Rating Scale and Supplement, Epworth Sleepiness Scale, Headache Impact Test, Neuropsychological Assessment Battery, Ohio State University –TBI Identification Method Interview Form, Post-Traumatic Checklist-5, Personal Health Questionnaire Depression Scale-8, Pittsburgh Sleep Quality Index, **Rivermead Post-Concussion Questionnaire-16 [PRIMARY OUTCOME MEASURE]**, World Health Organization Quality of Life Scale, and Medical/Psychiatric History.



Status (Updated July 2019)	Tampa	San Diego	Total
Prescreened	38	116	154
Screened	25	74	99
Screen Failures	4	21	25
Randomized	21	53	74
To be Randomized	0	0	0
In Treatment Phase	0	0	0
Early Termination	1	3	4
Completed	20	50	70
SAEs	0	0	0

Preliminary BLINDED Analysis:
The observed means (± SD) in RPQ-16 total score were 34.7 ± 11.7 (screening visit), 17.5 ± 12.7 (visit F1), and 15.1 ± 12.0 (visit F2), respectively. The mean improvements in RPQ-16 total score from an earlier visit to a later visit were 18.3 ± 13.2 (screening to F1), 20.7 ± 12.6 (screening to F2), and 2.2 ± 12.4 (F1 to F2). At visit F1, 68/72 subjects had improved in RPQ-16, and 53 subjects (74%) had improved by at least 8.5 RPQ units – the pre-defined clinically meaningful effect size. By visit F2, all 70 subjects had improved in RPQ-16, and 58 subjects (83%) had improved by at least 8.5 RPQ units. The improvement from F1 to F2 was only minimal. Twenty-four subjects (34%) actually got worse from F1 to F2, while 19 subjects (27%) showed improvement of 8.5 RPQ units or greater.

- Take Aways:**
- 1. Plan on 3-6 mos for IRB approvals on clinical trials.
 - 2. Recruitment will always be an issue – plan on advertising every 2-4 weeks.
 - 3. Off-base sites minimize downtime and maximize recruitment.
 - 4. Hire a clinical trials specialist to minimize surprise.
 - 5. Database housing is critical to the integrity and security of the clinical trial.

Treatment and funding sponsors are Wave Neuroscience (dba Newport Brain Research Laboratory) and Special Operations Command, Preservation of the Force and Family (POTFF). The Coordinating Center is based at The Uniformed Services University School of Medicine, Traumatic Injury Research Program.



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A specialized clinical/functional EEG/ERP/HRV protocol is conducted at the BL and F2 visits. The pre- and post-treatment electrophysiology assessment includes free running EEGs (eyes closed no task, eyes open no task) and cognitive event related potentials. Two ERP tasks are used: a visual three stimulus oddball task and an N-back task (N=0 and N=2). The EEG is recorded throughout the electrophysiological assessment and measures of heart rate variability are included in the analysis. EEG and ERP analysis include measures of inter-regional synchronization (synchronization likelihood and the weighted phase lag index), information dynamics (specific entropy rate and specific transfer entropy) and multichannel network analysis (Clustering Coefficient and Characteristic Path Length). It is hypothesized that the analysis of pre- and post-treatment brain electrical activity may offer insights into the underlying pathophysiology of persistent post-concussion syndrome that cannot be obtained from standardized patient report questionnaires.

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