Monitoring cognitively-impaired subjects in an interactive Internet-based clinical trial of a multi-factorial treatment based on a molecular model of chronic disease

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18yo

Autism-Asperger's
"We are seeing subtle but important changes."

"He is more willing to interact with us and recovers a bit faster from socially and physically stressing situations. His case manager asked if we are SURE Omni was accurately diagnosed. They are not used to seeing growth in these kids, only more successful adaptation and training."

15yo

Chronic Lyme, headache, myoclonus
"It is impossible to put into writing just how grateful we are for the MP."

"After one year on the MP, he can read, write and watch TV again. The tic is gone and headaches are 80% better. He is finally back in school and doing well."

53yo

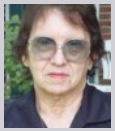
RA
"Mental fatigue and slower cognition, now improved and steadfast."

"I have had severe cognition problems (e.g. attention deficit disorder, problems switching tasks, emotional outbursts) defined as job threatening."

54yo

Sarcoidosis and RA
"My short term memory was nonexistent."

"I now work with contracts with the government in an Engineering capacity where recall is of paramount importance. Brain fog gradually dissipated through Phase 2."



71yo

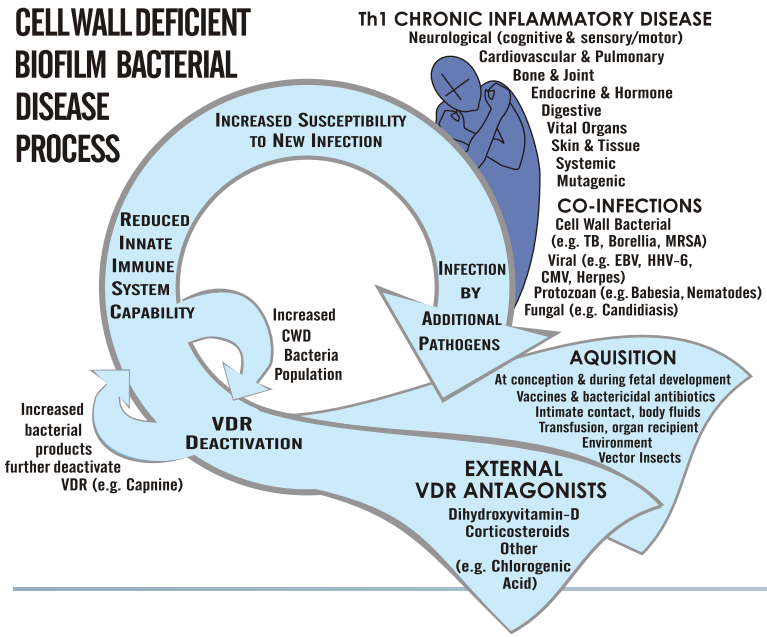
Lyme and RA
"The brain fog and lack of motivation and concentration are a thing of the past."

"The hardest symptoms to manage were probably all the brain fog and the dyslexia. The brain fog lifted first, then the dyslexia, and finally my level of motivation increased tremendously. I am so ambitious at the moment."

16yo

Chronic Lyme
"Her progress is simply amazing."

"Her reading ability is back. She does have to concentrate more to retain the information, but it is sticking. A year ago she couldn't read at all."



ABSTRACT The validity of a clinical trial is enhanced when all segments of a study population are represented. Based on this author's experience on an NIH Data, Safety and Monitoring Board, we were aware that most clinical trials exclude many of the sickest patients because they have diminished cognitive abilities, e.g. memory loss, poor communication skills, questionable judgment. Therefore, we designed a trial of a multi-factorial treatment for chronic disease in which cognitively-impaired patients could be adequately represented. The open trial of this therapy has resulted in the inclusion of a large number of patients with significant cognitive impairment. Nurses who monitor the progress of these cognitively impaired subjects are well-grounded in the molecular science to help them accurately assess the effects of the recovery process. Instruction of subjects and their participating physicians is done online. All communication between subjects and the nurses who monitor them is done in writing using a standard report form to collect data. Computer use, which is a new and daunting endeavor for many of the participants, adds a new tool to cognitive assessment. A standardized report form is used to facilitate accurate assessment and collect data. Regular reporting is expected to monitor comprehension and compliance with the protocol (which includes several medications) and to ensure early detection of medication error or unexpected treatment effects. Pertinent questioning solicits any important information that is excluded from the subject's report due to cognitive deficit, and rapid feedback by the nurses enhances subject safety. The ongoing reports are used to assess patient progress, especially in the area of improved cognitive abilities. We describe the observational skills needed, the assessment techniques used and the limits/advantages of monitoring subjects using this format. This unique method of observation has provided a level of monitoring equal to, and superior in some respects to that achieved by traditional methods (e.g. phone interviews or in-person visits) and has resulted in a fair representation of the cognitively-impaired patient in a ground breaking study.

"… using an open trial design may enhance participant recruitment and retention."

The effects of an open design on trial participant recruitment, compliance and retention--a randomized controlled trial comparison with a blinded, placebo-controlled design.

Health Services Research Unit, University of Aberdeen, Foresterhill, Aberdeen PMID: 16279289

"Virtual communities have the potential to meet the need to assist with monitoring activities, education."

Chronic disease management and the development of virtual communities.

Smith, AD Department of Management and Marketing, Robert Morris University, Pittsburgh, PA PMID: 18048306

"Use of a placebo-controlled design had a major effect on the dropout rates observed. … studies with alternative designs need to be considered."

Dropout Rates in Placebo-Controlled and Active-Control Clinical Trials of Antipsychotic Drugs A Meta-analysis Arch Gen Psychiatry. 2005

THE MARSHALL PROTOCOL IS A PHASE 2, OBSERVATIONAL, OPEN-LABEL STUDY OF:

Neurosarcoidosis
Parkinson's Disease
Systemic Lupus Erythematosus
Rheumatoid Arthritis
Multiple Sclerosis
Post Treatment Lyme Disease Syndrome
Bipolar Disorder
Obsessive-compulsive disorder
Fibromyalgia
Diabetes
Scleroderma
Chronic Fatigue Syndrome
Asperger's
Depression
Epilepsy
Migraines

MULTIFACTORIAL TREATMENT COMPONENTS OF THE STUDY:

- Reduce immunosuppression by secosteroid dihydroxyvitamin-D
- Enhance immune system with an angiotensin receptor blocker (olmesartan medoxomil)
- Eliminate intraphagocytic microbiota with low dose, pulsed antibiotics (minocycline, azithromycin, clindamycin)
- Limit stimulation of amygdala via incident radiation to eyes to prevent increased cognitive dysfunction

All instruction is provided on the study site with Tutorials, FAQs and written responses to questions.

All monitoring of the cohort is done by Nurses via weekly written reports using this standard format:

MP medication:
Palliative meds used this week:
Light exposure this week:
Symptoms rated 1-10:
Comments:
Plan for next week:
Questions:

Methods Nurses use to ensure study integrity:

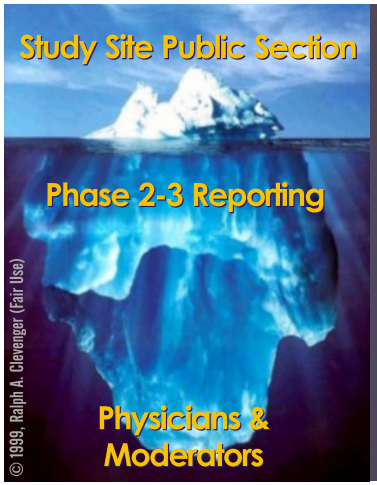
- Rapid feedback for each weekly report
- Answer subject's questions
- Repeat instructions as often as needed
- Ask leading questions to solicit pertinent information
- Provide directions tailored to member's level of cognition
- Require a detailed questionnaire after Phase One of the study
- Access to Phase Two restricted until cognition improves

Advantages of virtual monitoring:

- Unreported cognitive dysfunction is apparent when using the written medium
- Written reports provide a record of improved cognitive function

Limits of virtual monitoring:

- Visual observation is lacking
- Inexperience with computer may confound assessment
- Errant inferences may confound assessment



Execution of Phase 2 Study

Entry to Phase 2 by questionaire, then password only

6,594 Members
>250 Health Professionals
8,633 Topics
138,325 Posts
34,000 Visitors/month
500,000 Pages/month

Cognitive dysfunction self-reported or noted among cohort:

Memory loss
Diminished mental acuity (brain fog)
Labile moods
Learning disability
Poor concentration
Diminished intelligence
Poor problem solving, planning, organization, insight, reasoning

Evidence of cognitive dysfunction:

- Failure to follow study site instructions for posting
- Repetition of computer use errors despite instruction
- Failure to use the standard report form
- Misspelled words, poor sentence structure
- Failure to answer questions despite repeated requests
- Failure to report due to forgetfulness
- Failure to follow specific recommendations
- Expressions of frustration, irritability or anger

2/3 of the study site is restricted until cognition improves.

Cognitive function improvement is assessed by:

- Improvement in compliance with weekly reports
- Improved quality of report content
- Reports indicate that instructions are understood
- Reports indicate compliance with instructions
- Spelling and grammar improves
- Tone of reports is stable and positive
- Subject self-reports improved function

Recovery timeline:

Phase One takes approximately 3 months, Phase Two takes up to one year and Phase Three takes two years or more. Cognitive function improvement is seen after 6-12 months of therapy.