



The role of Prospective Strategies for a Possible Identification of Gadolinium Retention Issues

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Conflict of Interest

No conflicts of interest reported.

The role of Prospective Strategies for a Possible Identification of Gadolinium Retention Issues



- Q: Can effect of gadolinium retention in brain be ruled out?
- Primary safety endpoint: neuropsychological battery: (Functional, Cognitive, Behavior)
- A pre-specified threshold – challenging without clear signal
- Study population
 - Subjects requiring routine screening
 - At risk subjects (low vs high)
 - Diseased subjects (including, e.g., cancer with chemo)?
 - (Relatively) Healthy Volunteers (Q: taking questionnaires only or also receiving non-Gd enhanced MRI?)
- A prospective longitudinal cohort study with matched control – a master protocol approach

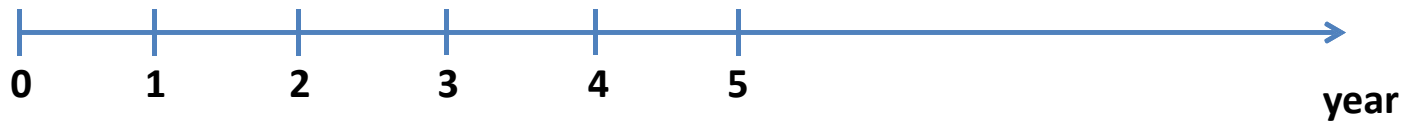
Registration (enrollment) period – Master Protocol

**Eligible Subjects Needing (Routine) Screening
(Inclusion/Exclusion)**



Data : age, sex, race, potential confounders (e.g., at-risk “low vs high”, disease ?),
 timings of repeated GBCA (allowing assessment of frequency of GBCA), etc.
 Data collection procedure such that dropouts can be minimized during follow-up
 Pre-specified risk margin?
 * CNTL1, CNTL2

Trial period – Trial Protocol



A Master Protocol Framework



- Multiple (8) GBCAs from 4 manufacturers
- Sharing of control arm across protocols
 - Concurrent control, external control or historical control
 - Imbalanced matching in settings with significant recruitment challenges
- Harmonized operational logistics, e.g., establish a trial network with infrastructure, streamlined enrollment process, and more
- Demographics, important baseline factors, potential confounders
- Model-based analysis methods for pooled analysis by body sites
 - If external control or historical control is used, can consider interim assessment of similarity between concurrent control and external control subjects



Sample Size Planning

A Theoretical Exercise

- Assumptions
- Change from baseline
- Rate of change
- Scenarios, e.g., by type of matched-control