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

Sue-Jane Wang, OB/OTS/CDER/FDA
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
Eligible Subjects Needing (Routine) Screening (Inclusion/Exclusion)

- CNTL*
- Gn1l-1
- Gn1l-2
- Gil-1
- Gil-2
- Gil-3
- Gmc-2
- Gmc-2
- Gmc-3

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

0 1 2 3 4 5

Sue-Jane Wang, OB/OTS/CDER/FDA

A Research Roadmap

NIH 02-15-2018
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