Real-world data in Alzheimer's disease

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Regulatory uses of real-world data (RWD) at FDA

- Characterize safety and use of an approved therapy in a broader population in the postmarketing setting
- Inform the design of clinical trials
- Confirmatory evidence to substantiate evidence of efficacy from a single adequate and well-controlled study
- In limited situations, may potentially serve as a control in a clinical trial

Common problems encountered with RWD

- No access to patient-level data
- Data is not fit-for-use
  - Missing data
  - Important study elements not captured in data source
- Assessments are not standardized
  - Differences in timing or collection of outcome measures between treated and control
- Protocol and analysis plan are not pre-specified
- Use of an inappropriate comparator
- Unmeasured confounding
- Problems with specification of the index date (“time zero”)

Use of RWD in drug development for Alzheimer's disease

- Randomized controlled trials are expected to establish efficacy for sporadic Alzheimer's disease
- RWD used to
  - Inform the design of clinical trials
  - Characterize safety and use of an approved therapy in a broader population in the postmarketing setting
- Post-marketing observational studies required for approved amyloid-targeted monoclonal antibodies (mabs)

Post-marketing Requirement for approved amyloid mabs

Conduct a registry-based, prospective, observational study to evaluate clinical safety outcomes among Alzheimer's disease patients treated with (amyloid-directed monoclonal antibody), using, for example, the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) registry, including patients who are ApoE ε4 homozygotes, and/or exposed to antithrombotics or thrombolytics, and/or have a diagnosis of, or imaging findings consistent with a high risk for, cerebral amyloid angiopathy. The primary clinical safety outcomes should include amyloid related imaging abnormalities (ARIA)-edema (ARIA-E), and ARIA-hemosiderin deposition (ARIA-H) and any associated clinical symptoms, and intracerebral hemorrhage >1 cm in size. Additional outcomes of interest should also include seizures, anaphylaxis, and death. Baseline characterization of the registry population should include demographic data, diagnosis and stage of disease, ApoE genotype, baseline MRI findings (e.g., microhemorrhages, evidence of cerebral amyloid angiography or other imaging findings consistent with high risk of cerebral amyloid angiography, etc.), other biomarkers that are potential predictors of disease course or adverse outcomes, and prior medications including prior Alzheimer's disease (AD) therapy and antithrombotic therapy. The registry should also collect information on concomitant medications (e.g., antiplatelet and antithrombotic drugs, other AD treatments). When available, the study should provide a comparison of safety outcomes to estimated background rates in an appropriate comparator population.

Study to be conducted over 10 years with yearly interim/progress reports.

FDA Guidances

Numerous FDA guidances on RWD/RWE available on the FDA website

https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence


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