Q1.

Part A

Observational design: Prospective cohort.
Experimental design: Hypothetical randomized controlled trial targeting the *VAR-X* pathway with a therapeutic.

Part B

For prospective cohort.
Study population is patient with Alzheimer's disease (with and without *VAR-X*).
Primary exposure is the presence of the gene variant *VAR-X*.
Primary outcome measure is the rate of cognitive decline.

For hypothetical randomized controlled trial.
Study population is Alzheimer's patient with *VAR-X*.
Primary exposure is therapeutic targeting *VAR-X* pathway.
Primary outcome measure is a change in the cognitive decline rate.

Part C

The hypothetical randomized controlled trial would provide the strongest evidence due to the randomization controlling for confounders. However, it may have ethical concerns because patients have the right to choose their treatment, but randomization makes sure that therapeutics are assigned randomly. Also, the treatment requires a study before use in humans, which is costly and time-consuming to ensure that the treatment is not harmful. While the prospective cohort is more feasible, cheaper, and ethical but is at risk of confounding and bias.

Q2.

Part A

The two impact biases are information biases due to loss to follow-up and confounding that influences both dependent and independent variables causing a false association such as age.

Part B

Strategies to minimize the impact of these biases and confounders include randomization and matching populations selection to prevent bias and confounders, and standardized data collection protocol to minimize information bias.

Q3.

Part A

Large-scale resources can be leveraged to perform a large retrospective cohort study by identifying Alzheimer's patients with genetic data for VAR-X and extracting cognitive decline information retrospectively.

Part B

Big data approaches gain statistical power and broader generalizability due to large sample sizes and diverse populations, which may increase external validity compared to traditional prospective cohorts. Challenges include data quality issues, misclassification, and missing data, which may reduce internal validity compared to traditional prospective cohorts