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Subject Recruitment and Retention Biases

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Randomized clinical trials require a random sample of subjects from the target population eventually to be treated. Any bias (systematic distortion) in the subject recruitment process may distort the study's results or make it non-generalizable to the target population. Similarly, any bias in the processes that cause subjects to leave the study may also affect the validity of the results. These biases may affect the entire study or only one arm of the study. Some biases may operate at individual sites, across all sites, or be caused by the absence of certain types of sites. Most people with these biases are not aware of them.

Clinical trials employ various measures to minimize these biases. For example, they use multiple investigators, randomize subject assignments to study arms, and blind the treatments. However, these measures may not eliminate the following sources of bias:

- **Volunteer bias.** Volunteers may have different characteristics than non-volunteers.
- **Membership bias.** Subjects more likely to respond to treatment, or more prone to safety issues, may differentially enroll. Different types of subjects (e.g., gender, age, ethnicity, language, disease severity) may answer eligibility questions differently or have different tolerances for the discomforts and inconveniences of the study.
- **Non-respondent bias.** Different types of potential subjects may have different response rates to subject recruiting efforts. Some may see study advertising, while others do not.
- **Geography bias.** Subjects of certain types may not be able to obtain practical transportation to a study site.
- **Cultural bias.** Different cultures have different attitudes towards clinical research.
- **Insurance bias.** Relatively healthy subjects may not be interested in or eligible to enroll because they have access to regular medical care.
- **Economic bias.** Low-income potential subjects may enroll in a study to obtain free medical care, or not enroll (or stay in the study) because they cannot afford the time off work. High-income people may enroll because they have leisure time, or not enroll because they consider their time too valuable.
- **Professional subject bias.** Subjects that actively supplement their income by participating in multiple clinical trials, perhaps with carry-over effects from one trial to the next, are relatively likely to enroll in a study.
- **Referral bias.** Different types of potential subjects may be more likely to be referred to the study.
- **Prevalence-incidence bias.** Potential subjects with chronic conditions are more likely to have the condition when a study is recruiting than potential subjects with temporary conditions.
- **Severity (progression) bias.** Potential subjects with more severe conditions may be differentially able and willing to enroll and stay in the study.
- **Survivor bias.** Potential subjects who die quickly are less likely to enroll and stay in the study.

- **Unacceptable disease bias.** Potential subjects with socially unacceptably diseases may not want to enroll in the study.
- **Hygiene bias.** Sites may not enroll qualified potential subjects because of poor personal hygiene, unpleasant personalities, or other similar factors.
- **Apprehension (white coat hypertension) bias.** Different types of potential subjects may have more anxiety, causing ineligible heart rate and blood pressure readings.
- **Pleasing bias.** Different types of potential and enrolled subjects may be differentially interested in pleasing the investigator or study coordinator.
- **Expectation bias.** Different types of potential and enrolled subjects may have different expectations of the study, and enroll or withdraw at different rates.
- **Consent bias.** Potential subjects who are able to understand informed consent information may have higher retention rates.
- **Recall bias.** Subjects may selectively forget about prior events, e.g., unpleasant procedures or symptoms.
- **Workup bias.** Study personnel may become more proficient during the course of the study, causing differences in early and late enrolling populations.
- **Observer bias.** Sites may interpret eligibility criteria and conduct screening tests differently.
- **Equipment bias.** Test equipment may be out of calibration in a way that applies differently to different types of subjects and potential subjects.
- **Assessor bias.** Assessors may collect and interpret data differently for different types of potential subjects. They may modify their interpretation of test results if they know the results of prior tests for different types of potential subjects.
- **Lab bias.** Testing labs may generate different results versus their reference ranges.
- **Aim-to-please bias.** The site may, consciously or unconsciously, selectively recruit subjects to generate results that it thinks the sponsor wants to see.
- **Competing studies bias.** The site may selectively enroll certain subjects in one study and others in another study.
- **Attention bias (Hawthorne effect).** Different types of potential subjects may respond differently because they know they are being measured.
- **Adverse Event Bias.** Different types of subjects may have different rates and severities of adverse events, affecting their retention.
- **Withdrawal bias.** Subjects who do or do not withdraw from the study may have different characteristics.

Protocol designers and study managers should consider these potential biases when writing eligibility criteria and study timelines, and recruiting research sites. Once the study is underway, statisticians should monitor the characteristics of enrolled and withdrawn subjects to detect any biases in the study population. It may be possible to guide sites to correct the biases, conduct targeted advertising programs, or recruit new sites with appropriate populations. It may be necessary to revise the protocol or limit future marketing claims.

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