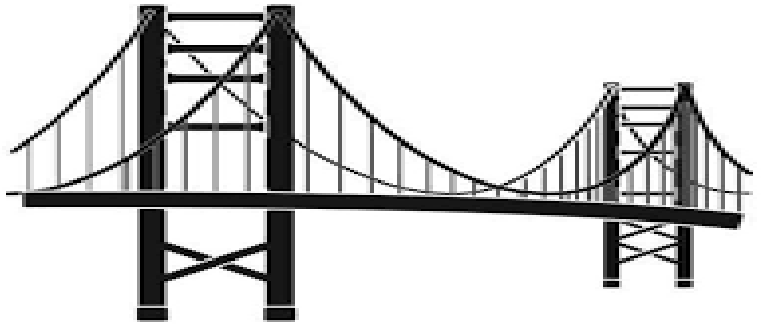
Partners in Progress
Cancer Patient Advocates and FDA Public Workshop III

Clinical Trial Population



Real World Patients

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Outline

I. Clinical Trials (CTs)

- Purpose
- CT sponsors
- General designs in oncology
- FDA use of CT data

II. Potential limitations of CTs

- Study population may differ from general population with the disease
- Design/Size

III. Addressing limitations of CTs

I. Improving representativeness and generalizability of CT results

II. Study designs

Clinical Trial Basics

- **Purpose**
  - **Definition:** A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes

    -National Cancer Institute

Clinical Trial Sponsors

- **Federal agencies/institutes**
  - National Cancer Institute (National Institutes of Health [NIH]
  - Dept of Veterans Affairs
  - Department of Defense
- **Academic medical centers**
  - Single or multiple institutions
  - Consortiums
- **Cooperative groups**
- **Pharmaceutical companies**
- **Patient advocacy groups**

Clinical Trial Designs in Oncology

- **Randomized**: comparing 1 or more investigational treatments to a control or standard
- **Single arm**: no comparison; evaluating safety, evaluating dose, anti-tumor activity
- **Complex, innovative designs**
  - Evaluating multiple drugs in single trial, with single tumor type/biomarker
  - Comparing single drug across several tumor types/biomarkers
- **Others**: non-interventional- Observational, natural history

Uses of Clinical Trial Data

- Support approval decisions
  - Efficacy
  - Safety
  - Balance of benefit: risk
- Evaluate sequencing of therapies
- Post-approval studies
  - to obtain longer-term data in safety, efficacy, etc
  - to support different dosing strategies
  - to support use in other populations

Potential Limitations of Clinical Trial Data

- Study population may differ from general population with the disease
  - Demographics (race/ethnicity, age)
  - Eligibility criteria (performance status, organ function, brain metastases)
  - Selection bias- CT patients may have less aggressive disease
  - Regional differences in:
    - available therapies, practice patterns, quality of care during treatment
    - etiologic risk factors (e.g., liver cancer, head and neck cancer, etc.,)
- Trial Design Issues
  - Size of trial (especially in oncology)
    - may not permit broad representation
    - may not permit analyses of outcomes in relevant subgroups
  - Single trial may not answer all relevant questions

‘Representativeness’ and ‘Generalizability’

- **Representativeness:**
  - are the results of the study true, or are they an artifact of the way the study was designed or conducted; i.e., is the study is internally valid?

- **Generalizability:**
  - are the study results likely to apply, generally or specifically, in other study settings or samples; i.e., are the study results externally valid?

Example: Underrepresentation by Age

- Older adults proportionally underrepresented in oncology clinical trials
  - lacks robust knowledge of the risks and benefits of cancer treatments in older adults, especially those over age 75
- Age-related physiologic changes in older adults can affect:
  - pharmacokinetics
  - pharmacodynamic response to the drug
  - comorbidities

Example: Underrepresentation by Race/Ethnicity

- Racial and ethnic minorities underrepresented in oncology trials
- Differences in ancestry may portend different incidence of genomic profiles
  - EGFR mutation in lung cancer
- Genetic differences may have relevancy to
  - Drug metabolism
  - Environmental/dietary factors
- Access to potentially effective therapy may only be feasible on CT

Improving Representativeness & Generalizability

- **Clinical Trial Level**
  - Broadening eligibility criteria (e.g., organ function, prior therapies, etc.,)
  - Broad representation across demographic factors (race/ethnicity, age, etc.,)

- **Drug development strategies**
  - Use of alternate trial designs
    - 'Pragmatic' or hybrid trials (e.g., decentralized clinical trial)
    - Inclusion of separate cohorts (on basis of organ function, age, more advanced disease, etc.,)
  - Use of non-clinical trial data sources (real world data/real world evidence)
  - Investigator-facing strategies
    - Diversity in clinical trialists and supportive staff, cultural competency training, etc.,

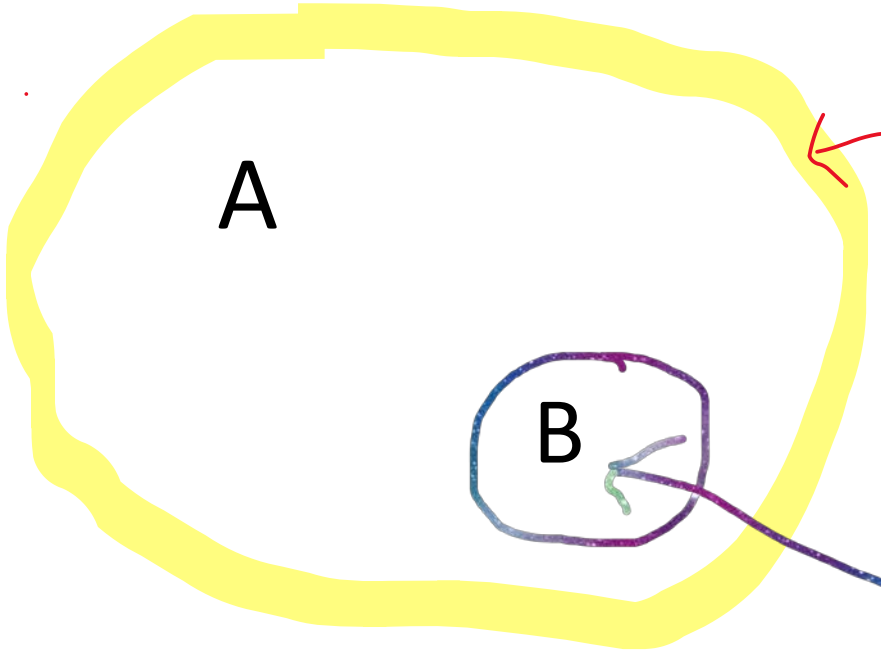
Decentralized Clinical Trials

- Terminology ('virtual,' 'patient-centric,' etc.,)
  - moving prospective data collection "outside the brick and mortar boundaries of traditional clinical research facilities"

- Potential advantages:
  - facilitate recruiting, enrolling and retention of study participants
  - reduce administrative burdens on sponsors and investigators
  - permit patients to receive treatments from community providers without compromising the quality of the study or the integrity of data.
  - leverages use of technology: wearables, tele-health visits, online patient diaries, e-informed consent programs, and other tools
  - access to expanded sources of evidence from lab tests, insurance claims, etc.,

- Potentially useful to enroll diverse populations, patients with rare diseases

Evaluating Relevant Subgroups in Single Trial



Basis for primary efficacy analysis (i.e., omit B)

Nested cohort (e.g., organ dysfunction, lower performance status, etc.,)

Real World Data/Real World Evidence

- Data obtained outside a clinical trial setting

- Sources may include: electronic medical records, health insurance claims, registries, etc.

- Use of RWD/RWE:
  - for postmarket monitoring of the safety of products
  - for efficacy assessment
    - data from registries, natural history studies and chart reviews -- to establish a comparison arm in single arm trials in oncology and rare diseases

FDA Strategic Framework

- Guidance
- Engagement
- Research
- Policy

THANK YOU!!