Role of Clinical Trials in Cancer Research

- Patient participation in clinical trials forms the backbone of cancer clinical research.
- Clinical trials are the key step in advancing new treatments and improving outcomes.
- It is commonly assumed that only 2%–3% of adult cancer patients participate in clinical trials.
- Most Americans view clinical trial participation favorably.
Patient Participation in Clinical Trials

- Clear gap between the willingness of patients to participate in trials and their actual participation rates
- Suggests there are numerous barriers to trial participation which may be modifiable
- Barriers to trial participation have been the subject of much research, with a major emphasis on patient-related barriers
- This emphasis often interpreted to indicate that patients are the primary limiting factor to improving trial enrollment
Figure 1: Cancer clinical trial decision-making framework*

Demographic and socioeconomic disparities

Spanning the entirety of the trial decision-making process

* Unger et al., JNCI, 2019
Structural Barriers

Access to a clinic:
- Influenced by:
  - Availability of transportation
  - Travel costs
  - Insurance status
  - Child care
- Uninsured or underinsured patients present with later stage of disease
  - Relationship to comorbidities

Absence of an available trial:
- Study is available but not at patient’s site
  - Requires travel to participate, a major burden for many patients
- Rare cancer
  - Investment in new treatment not a priority given finite resources

Clinical Barriers

- Even if a trial is available, patients may not be eligible
- Trial eligibility attempt to satisfy opposing factors:
  - Sufficiently narrow so that treatment effect is ~constant
  - Sufficiently broad so trial results apply to a meaningful population of patients
- Trials often criticized for having narrow eligibility criteria, sacrificing generalizability and reducing access for patients
- Presence of comorbid conditions
  - Dominant reason for ineligibility exclusions (60% of trial eligibility criteria)
- ASCO, Friends of Cancer Research, and the FDA recently published recommendations to modernize eligibility criteria
Physician’s Role

- In their vital role guiding patient care, physicians may prefer a specific treatment.

- Trial participation can interfere with physician-patient relationship.

- Practical considerations:
  - Time and effort can be burdensome
  - Reimbursement

- This removes a key opportunity for eligible patients to participate in a trial.
Patient Attitudes & Decision-Making

- Ultimate decision rests with the patient
- Motivated by both altruism and finding best treatment for their cancer
- Patients uneasy or fearful about trial participation
- Residual mistrust of medical science due to past abuses
  - e.g. Tuskegee Syphilis Study, human experimentation with radiation after WWII
- Modern attention to patient protections and informed consent has reduced fears for many
  - Belmont report (1979): Respect for Persons, Beneficence, and Justice
Fear of experimentation expressed through a dislike of randomization

Specific treatment related concerns, including:
- Random treatment
- Participation in a research protocol
- Didn’t want the protocol treatment
- Treatment side effects
- Treatment not right for them

Other notable barriers:
- Friends and family opposed
- Burden to family
- How to pay for treatment
- Lack of trust of staff or quality

*Unger et al., JCO, 2013*
Rationale and Objective

- Key Concern: The rate of trial participation has not changed substantially over time
  - Over emphasis on patient-related barriers?

- Few studies have characterized the entire trial decision-making process with respect to trial barrier domains

- Understanding the magnitude of trial barrier domains is important to guide policy regarding research/resources to improve trial participation

- We examined the magnitude of domains of trial barriers by synthesizing prior research under a uniform framework for barrier domains
Methods

- Systematic review and meta-analysis (PRISMA)

- Inclusion criteria:
  - Domestic U.S. studies only
  - Fully documented trial decision-making process
  - Studies representative of the general cancer population

- Weighted estimates according to the proportion of patients expected to received cancer care in the academic (15%) vs. community (85%) settings
Figure 2. Selection of studies included in the analysis*

- 13 studies with n=8,883 patients
- 9 studies focused on academic care settings
- 4 studies focused on community care settings

* Unger et al., JNCI, 2019

**Systematic Review and Meta-Analysis: Results**

- PUBMED, n = 1,920
- Google Scholar, n = 6,060
- Web of Science, n = 389
- Ovid Medline, n = 1,306 (1,648 results, 342 duplicate observations)

Total, n = 9,675

- Duplicates excluded, n = 2,099
- Titles / abstracts screened, n = 7,576
- Other topics, n = 7,538
- Full articles searched, n = 38
- Only overall enrollment assessed, n = 5
- Only patients with available trials, n = 6
- Not representative of patients, n = 2
- Multiple observations per patient, n = 1
- Data inconsistencies/ incompleteness, n = 4
- Missing availability or eligibility, n = 2
- Surveyed willingness to participate only, n = 3
- Non-US setting, n = 2

Included in final analysis, n = 13

Presented by: Joseph Unger, PhD
Figure 3. Magnitude of barriers for each domain for academic sites, community sites, and all sites combined*

* Unger et al., JNCI, 2019
Discussion

- This was the first effort to systematically both define and quantify domains of clinical trial barriers.

- Results reveal that more than half (55.6%) of all cancer patients did not participate in trials because no trial was available.

- When a trial was available, an additional 21.5% were ineligible.

- These **structural and clinical factors** are the reasons more than three of four patients (77.1%) did not participate.

- In contrast, patient-related factors and patient choice comprised only a small portion of barriers to trial participation overall:
  - When eligible patients are offered a trial, they agree to participate half the time.
Discussion

- The overall trial participation rate was 8.1%, much higher than the 2%–3% rates typically assumed
  - Likely due to the contributions of industry-sponsored trials (2:1)

- But the rate remains low with numerous adverse consequences:
  - Trials often fail to complete due to poor accrual
  - Trials take a very long time to complete, generating less timely and less influential results

Presented by: Joseph Unger, PhD
Conclusions

- Enormous need to address structural and clinical barriers to trial participation

- Focus should be to improve access to available trials:
  - Improved outreach to community oncologists and their patients
  - Improved use of portals to identify recruiting trials (i.e. cancer.gov)
  - Providing patients of all income levels the resources to travel to participate in available trials

- Only by addressing structural and clinical barriers will the participation rate in cancer treatment trials be increased in a substantial way