Canadian Cancer Trials Group

Clinical Trial Design and the Real World: Efforts to Broaden Applicability

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Disclosures

Pfizer

Celgene

Hecht Foundation

CBCF

CIHR

AstraZeneca

Learning Objectives

- To describe the pivotal role of eligibility criteria in clinical trial research and the rationale to broaden them
- To categorize eligibility criteria in clinical trials evaluating anticancer therapy
- To list specific recommendations from the American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement to broaden eligibility criteria

Clinical Trials: Current Status

- Clinical trials are pivotal to drug development and advancement of care
- Multiple challenges to conduct exist
  - Resource consumption
  - Timelines for conduct
  - Applicability and uptake of results by clinical community (real world)

Eligibility Criteria: Role in Trial Conduct

- Identify the population appropriate for enrollment
  - Unmet needs in clinical care; disease state
- Protect participants: safety and rights
- Establish the data requirements (type of data and means of collection) to meet the research objectives
  - Treatment efficacy
  - Toxicity/ tolerability
  - Correlative studies

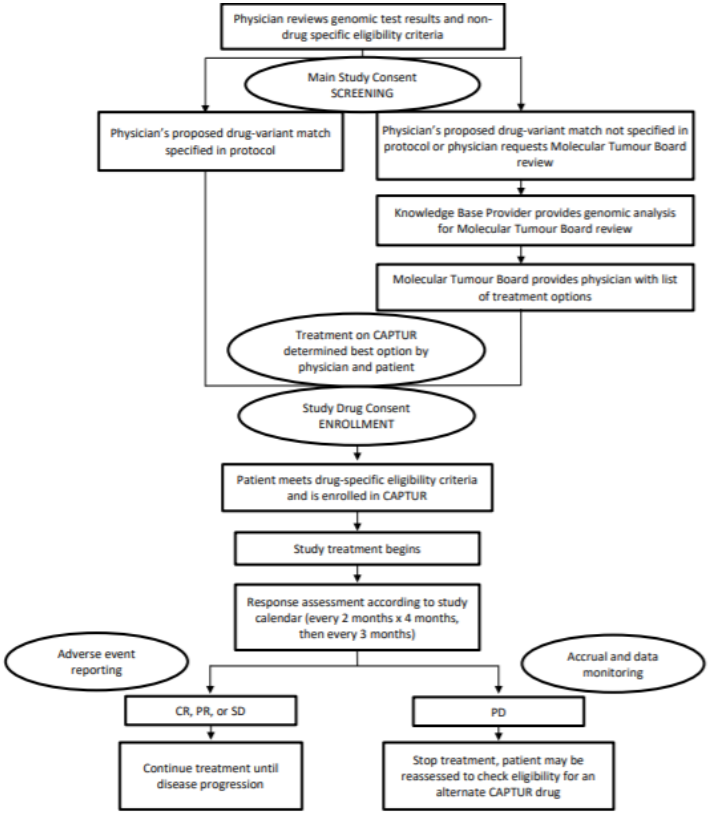
Eligibility Criteria Categories

Category	Examples
Disease	Histology; extent of spread, prior treatments
Patient Characteristics	Age, sex, performance status, life expectancy
Co morbities	Prior/ concurrent malignancies, major medical problems, chronic disease states, concomitant medications
Organ function	Renal, hepatic, cardiac function
Intervention related	Credentialing of sites, investigators
Data collection related	Questionnaires, tissue submission
Ethics/ regulatory	Ethics Board approval, consents

Modern Clinical Trials: More Complex Eligibility Criteria/ Procedures

- Targeted therapeutics and advancements in technologies for molecular characterization of tumours have led to new trials designs
- Biomarker Platform Trials
  - Basket design: evaluation of activity of a single drug directed against a specific mutation (s), agnostic of histology
- Umbrella design: evaluation of activity of multiple drugs directed against different mutations, common histology
- Rare histology trials

CCTG PM.1 Canadian Profiling and Targeted agent Utilization tRial (CAPTUR)
A Phase II Basket Trial (NCT03297606)



Sample Size: 24 patients per cohort
Maximum 30 cohorts (720 patients)

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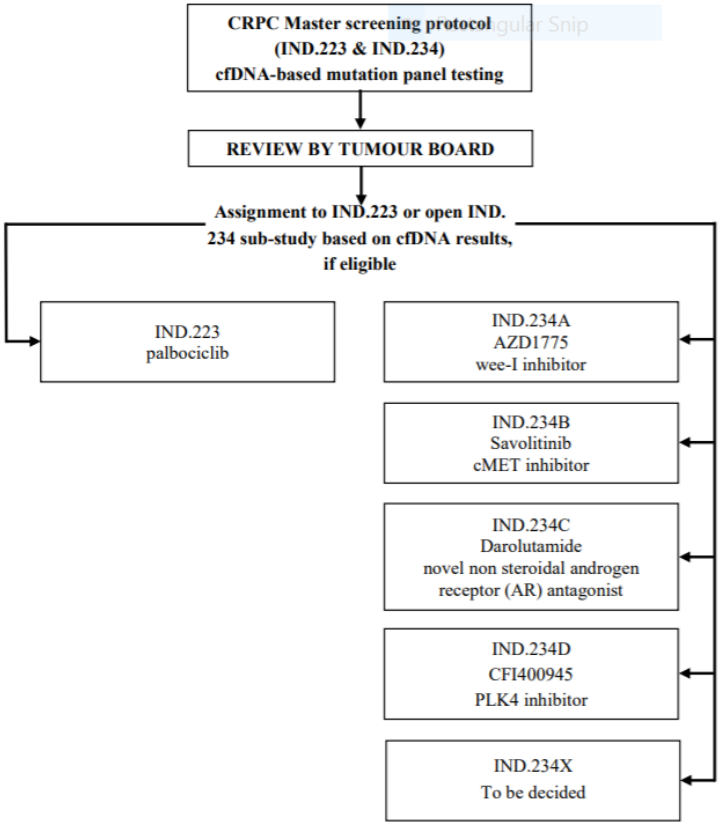
CCTG IND 234: Prostate Cancer Biomarker Enrichment And Treatment Selection (PC-BETS) Study (NCT03385655)



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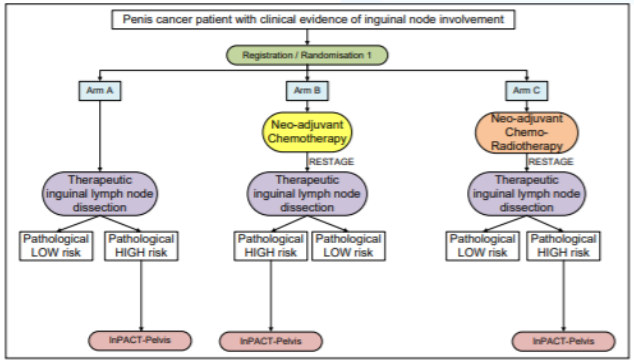
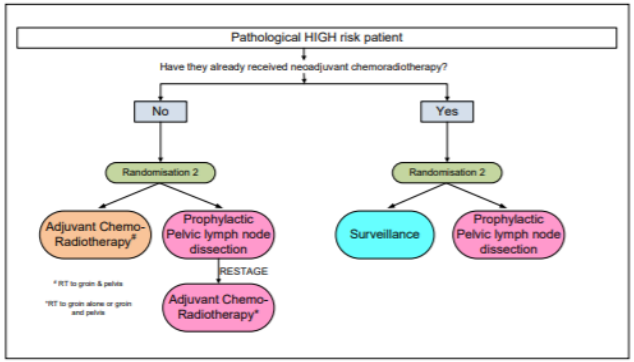
InPACT: International Penile Advanced Cancer Trial
NCT02305654

TRIAL SCHEMA

InPACT-neoadjuvant



InPACT-pelvis



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Broadening Eligibility Criteria: Rationale

- Enhance enrollment
- Enhance efficiency of trial conduct – faster timelines and data for future studies
- Enhance applicability to clinical practice

Eligibility Criteria Initiative

- Collaborative effort: ASCO, Friends of Cancer Research and US FDA
- Examined eligibility criteria in 5 categories
  - Brain metastases
  - Minimum Age
  - HIV infection
  - Organs dysfunction
  - Prior and concurrent malignancies
- Developed consensus recommendations for protocol text

Brain Metastases

- Patients with treated and or stable brain metastases should be routinely included; routinely excluded only if compelling reason(s)

- Patients with active (untreated or progressive) brain metastases not be automatically excluded – consider natural history of disease, trial phase and design, drug mechanism of action, PK and potential CNS penetration

- May be appropriate to exclude leptomeningeal disease due to poor prognosis but consider exceptions; explicitly list as exclusion criteria

Minimal Age for Enrollment

- Dose finding trials; pediatric- specific cohorts should be included if strong likelihood of benefit; use staggered enrollment starting with older children

- Late phase trials in diseases/ therapeutic target that span age spectrum: include pediatric and adolescent patients; consider enrolling patients <12 years with proper support and expertise

HIV Infection

- Healthy patients with cancer with HIV infection and low risk of AIDS related outcomes should be included unless specific rationale to exclude exists

- Eligibility criteria should focus on current and past CD4 and T cell counts, history of AIDS-defining conditions and status of HIV treatment; treat with same standards as patients with other comorbidities; consider standard antiretroviral therapy ART) as a concomitant medication; follow treatment guidelines for ART

Organ Dysfunction

- Renal function criteria should be based on creatinine clearance rather than creatinine; use liberal criteria (eg, >30 ml/min) if renal excretion not significant

- Hepatic function (eg, AST, ALT, bilirubin) criteria should be relative to institutional normal ranges rather than universal cutoff values

- For non cardiotoxic therapies, do not impose arbitrary ejection fraction values; if required, use a validated clinical classification system (e.g. New York Heart Association); eliminate ECG monitoring in late phase trials if cardiac risk not a concern

Prior and Concurrent Malignancies

- Include patients with prior or concurrent malignancies, especially if natural history/ treatment does not have the potential to interfere with safety or efficacy assessment of trial therapy

Examples of Design Considerations

- Enroll specific cohorts of patients traditionally excluded from trials
- Assess safety, tolerability and pharmacokinetics separately in specific population
- Stratify enrollment to include specific population
- Adapt enrollment after analysis of initial data in specific population and recommendation of oversight committee (DSMC)
- Consider companion protocol restricted to specific population

Conclusions

- Eligibility criteria are pivotal in the conduct of a trial and applicability of results to clinical practice
- Strong rationale for broadening eligibility in cancer clinical trials
- Criteria related to brain metastases, minimum age, HIV infection, organ function and prior/ current malignancies should be appropriate to the trial design and research question
- Onus on protocol authors to justify excluding specific patient populations from clinical trials
- Specific trial designs may be used when enrolling specific patient populations previously excluded from trials

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Thank You

References

- Kim ES, Bernstein D, Hilsenbeck SG, et al: Modernizing eligibility criteria for molecularly driven trials. J Clin Oncol 33:2815-20, 2015.
- Beaver JA, Ison G, Pazdur R: Reevaluating eligibility criteria: Balancing patient protection and participation in oncology trials. N Engl J Med 376: 1504-05, 2017.
- Kim ES, Bruinooge SS, Roberts S et al: Broadening eligibility criteria to make clinical trials more representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement. J Clin Oncol 35: 3737-44, 2017
- Lin N, Prowell T, Tan A, et al: Modernizing clinical trial eligibility criteria: Recommendations of the American Society of Clinical Oncology-Friends of Cancer Research Brain Metastases Working Group. J Clin Oncol 35:3760-73, 2017
- Gore L, Ivy P, Balis F, et al: Modernizing clinical trial eligibility: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research Minimum Age Working Group. J Clin Oncol 35:3781-87, 2017
- Uldrick TS, Ison G, Rudek MA, et al: Modernizing clinical trial eligibility criteria: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research HIV Working Group. J Clin Oncol 35:3774-80, 2017
- Lichtman SM, Harvey RD, Damiette Smit MA, et al: Modernizing clinical trial eligibility criteria: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research Organ Dysfunction, Prior or Concurrent Malignancy, and Comorbidities Working Group. J Clin Oncol 35:3753-59, 2017