# Overview

Potential applications of exploratory subgroup analyses:

1. Many subgroups are pre-specified (mandated) as in HTA
2. Subgroups pre-specified in Ph3 testing (and/or forest plots) may be further scrutinized
3. Are there strategic opportunities to pro-actively explore subgroups? (
   * Replace with MRCTS)
   * Put (3) below here

The statistical principles for robust inference and decision-making are essentially the same but depends heavily on the ultimate interpretation -- or rather risk of over-interpretation -- which may evolve and depend on the audience

* How to conduct principled subgroup analyses?
* Where and when to be pro-active and re-active?

1. When many subgroups are pre-specified as in HTA applications (PICO’s) the issues of robustness are extreme as erroneous decisions would be “virtually guaranteed” if basic confidence-intervals are over-interpreted (e.g., across 20 small sub-populations within a country)
   1. Opportunities for rigorous adjustment may be limited, however quantifying and communicating the risks can be feasible
2. Biomarker subgroups (pre-specified testing) or subgroups evaluated in pre-specified forest plots may be further scrutinized by regulators with implications for the approved population
   1. Regulators may conduct sub-optimal analyses and over-interpret findings
   2. Should we pro-actively evaluate to inform team strategy, applying demonstrable statistical rigor
3. Are there scenarios where a restricted label could be advantageous? If a majority subset of the overall population can be identified, where a more enhanced treatment benefit (e.g. 80-90%) can be established, could this lead to a higher-tier reimbursement and synergy in use within clinical practice

# Exploratory subgroup applications

While pre-specified subgroups provide a higher level of evidence than post-hoc analyses there could be important subgroups based on patient characteristics that are not anticipated or well understood. We investigate approaches for subgroup identification to evaluate the feasibility of conducting *exploratory subgroup analyses* in a rigorous manner under various settings with focus on oncology.

* *Phase 2* Applications:
  + Realistically, only *substantial heterogeneous treatment effects* (HTE’s) can be identified and well estimated under Ph2 settings
  + Identification of large effects based on single factors and/or two-factor combinations (e.g., Histology and PD-L1 CPS) could be informative for Ph3:
    - Testing strategy; Randomization stratification; Forest plot subgroup specifications.
  + Potential to inform biomarker populations: Subgroups based on pre-specified cuts as well as evaluations based on continuous biomarkers
* *Phase 3* Applications:
  + While moderate effects may be feasible in Ph3, identification of substantial HTE’s is generally more robust and practically actionable
  + Out of scope are alpha-adjusted subgroups
  + Standard (pre-specified) **forest plot** results may suggest potential lack-of-benefit in *a subgroup*
    - Case examples (Amatya et al. 2021) of approvals in the “ITT population despite decreased treatment effect in an important subgroup” as well as approvals in subgroups
      * The underlying theme in these regulatory reviews was the assessment of an apparent detrimental effect, the evidence for potential harm and biological plausibility
    - A comprehensive evaluation of subgroups – targeting large effects – may identify a more detailed (*alternative HTE subgroup*) structure than the pre-specified subgroups of the *forest plot*
  + In **MRCTs** the establishment of consistency in regional studies may be challenging
    - Evaluation of HTE’s in the global trial is a suggested first step to inform the evaluation of the regional study
    - Consistency may not be met for the overall population (e.g., in China or Japan), however for “subgroup A” (identified in the global trial) consistency may potentially be demonstrated

In general, for both Phase 2 and Phase 3 settings the identification of large effects (negative or positive) could have the most potential pragmatic impact; “Lack of benefit, or mild benefit” may not be sufficient reason to recommend against treatment or to exclude from inclusion in future program development. In the case of an existing detrimental subgroup, the complementary population may potentially be considered to derive benefit with a “higher degree of confidence” relative to the overall ITT population.

Amatya, Anup K., Mallorie H. Fiero, Erik W. Bloomquist, Arup K. Sinha, Steven J. Lemery, Harpreet Singh, Amna Ibrahim, et al. 2021. “Subgroup Analyses in Oncology Trials: Regulatory Considerations and Case Examples.” *Clinical Cancer Research* 27 (21): 5753–56.