Analysis Using Intent-to-Treat versus Per Protocol Reviews in Pragmatic Clinical Trials

Michael Rothe, MS; Mallory Connors, CCDM; Amber Boose, MPH; Pam Mangat, MS; Liz Garrett-Mayer, PhD

American Society of Clinical Oncology (ASCO)

May 20, 2025

Disclosures and Disclaimers

- I am an employee of the American Society of Clinical Oncology (ASCO).
  - ASCO receives funding from the following pharmaceutical companies to support the TAPUR Study: AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly and Company, Genentech, Merck, Pfizer, Seagen, now a wholly owned subsidiary of Pfizer Inc, and Taiho Oncology.
- All opinions expressed here are my own and not necessarily those of ASCO.

Statement of Purpose

- The aim of this presentation is to describe:
  - The utilization of a decision making flowchart to determine whether participants can be replaced in a pragmatic clinical trial
  - The benefits for replacing participants in pragmatic clinical trials

Primary Endpoint Analysis

- Simon's optimal two-stage design with H_0=15% vs H_a=35%, power: 80%, and α: 0.10.
- 10 participants enrolled in stage I. If fewer than two participants have met the primary endpoint, the cohort is permanently closed for futility, otherwise the cohort expands to stage II.
- 18 additional participants enrolled in stage II. The null hypothesis is rejected if at least seven participants out of 28 have met the primary endpoint.
- Primary endpoint is disease control (DC) defined as complete or partial response or stable disease of at least 16 weeks duration measured using RECIST criteria.

Evaluability Review Process

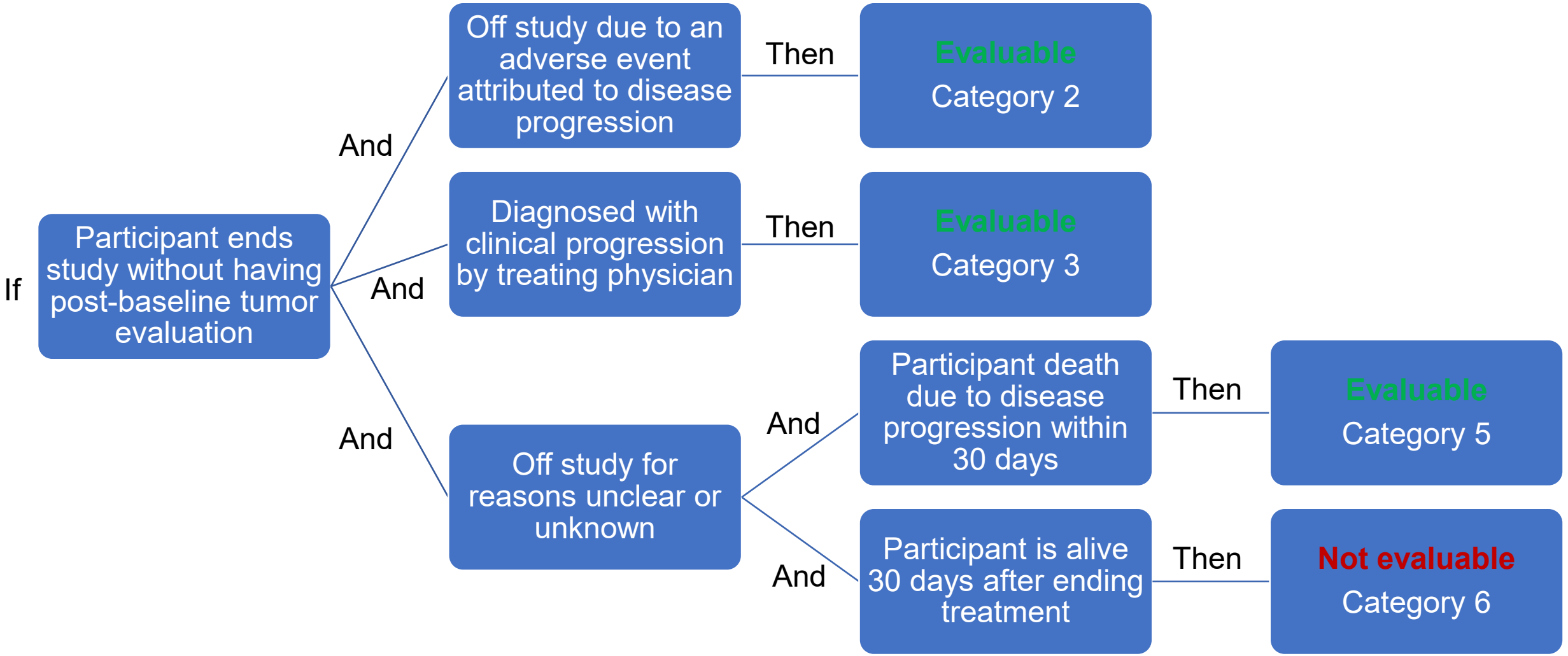
- Any participant determined to not be evaluable can be replaced.
- Follows a clearly defined flowchart developed by the Study Statistician and reviewed by the DSMB.
- The same criteria are applied to all participants in all cohorts equally.
- Reviews occur prior to the analysis of a cohort and before the DC rate is known for the cohort.

Evaluable Participant Criteria

Logic	Order	Category	Form/Variable	Evaluability/ Replacement
IF	1	Participants who - have no post-baseline tumor evaluation, AND - indicate PD as primary reason for leaving the study	- ENDSTUD - No post baseline EVAL	Evaluable, PD. Do not replace
ELSE IF	2	Participants who - have no post-baseline tumor evaluation, AND - leave the study due to tumor/disease (tumor related AE/SAE)	- AE/AEFU narrative - ENDSTUD Question F2 and narrative	Evaluable, PD. Do not replace
ELSE IF	3	Participants who - have no post-baseline tumor evaluation, AND - leave the study and are assessed as having clinical/symptomatic PD by the site	currently - ENDSTUD narratives and Emails - but would like to change to ENDSTUD	Evaluable, PD. Do not replace

Replacement Rules

- Participants with post-baseline tumor evaluations are evaluable based on those measurements.
- Participants with any evidence of disease progression cannot be replaced.
  - Tumor progression or clinical progression entered on the end of study form.
  - Adverse events related to disease progression.
  - Participants who die within 30 days of leaving study due to disease progression.
- Replaced participants are not removed from the study.
  - Replacement is for the primary endpoint analysis only.
  - All participants are included in safety analyses.



Why Develop an Evaluability Review Process?

- Pragmatic trial
  - Primary endpoint reliant on scans or disease assessment
  - No requirement for end of study tumor scans and some participants end study with only a baseline scan
  - Small sample sizes with inferences based on a small number of participants
- Participants with advanced disease
- Working with FDA approved drugs

Analysis Comparison

	Intent-to-treat	Evaluability Reviews
Participant with no primary endpoint data	No tumor response. Included in primary outcome analysis.	Reviewed in flowchart. May or may not be included in analysis.
Participant completed study	Completed per protocol.	Evaluated to determine whether study was completed per protocol.
Small sample size and population with advanced disease	May impact statistical integrity.	Reduces bias and provides consistent objective determination.

Limitations

- Requires drafting an extensive flowchart that encapsulates all possible outcomes that deviate from protocol defined endpoints, and revision may be required as new use cases arise.
- Adds work, as someone on the study team will need to review participants to determine whether they should be included in the primary outcome analysis.
- May delay the trial, if the final participant enrolled needs to reach a certain timepoint for data maturation before any decisions regarding replacement can be made.
- Unlikely to be appropriate for registration trials.

Conclusions

- Implementation of an evaluability review process that allows replacement of participants can help to maintain the statistical integrity of pragmatic trials with small sample sizes.
- The process should always be based on a clearly defined flowchart, and any participant with evidence of not reaching the primary endpoint should always be included in the primary analysis.

Thank you!

- Questions? Please contact TAPUR@asco.org
- The authors thank the patients who participated, the clinical centers, staff, and the TAPUR Study Team for study conduct and support
- Published TAPUR cohorts are now available on the ASCO Data Library

ASCO's Available Datasets

https://asco.org/research-data/asco-data-library

Targeted Agent and Profiling Utilization Registry (TAPUR) Study data

The TAPUR study is a phase II, prospective, nonrandomized basket clinical trial that aims to describe the safety and efficacy of commercially available, targeted anti-cancer drugs prescribed for treatment of patients with advanced cancer that has a potentially actionable genomic variant. TAPUR uses a Simon two-stage design to study Food and Drug Administration (FDA)-approved targeted therapies that are contributed by collaborating pharmaceutical companies, catalogue the choice of molecular profiling test by clinical oncologists and develop hypotheses for additional clinical trials. Data collected for the TAPUR Study include clinical and genomics data across non-randomized arms or cohorts. All participants who receive treatment with a drug available in the protocol are followed for standard toxicity and efficacy outcomes including tumor response, progression-free and overall survival as well as duration of treatment and high grade or serious adverse events.

Dataset Description (pdf) | Data Dictionary (pdf) | TAPUR Study Visit Schedule (pdf)

ASCO COVID-19 Registry Data

The ASCO Survey on COVID-19 in Oncology Registry (ASCO Registry) aims to help the cancer community learn more about the patterns of symptoms and severity of COVID-19 among patients with cancer, as well as how COVID-19 is impacting the delivery of cancer care and patient outcomes. The ASCO Registry collects baseline and follow-up data on how the virus impacts cancer care and patient outcomes for up to two years after a patient with cancer is infected with SARS-Cov-2. Explore the information further using two data visualization tools – the ASCO Registry Dashboard and Interactive Map of Oncology.

Meeting Abstracts

Meeting abstracts represent a full accounting of the research presented in oral or poster form at ASCO meetings over the past 40 years and reflect the state of the science as well as changes in oncology over the last few decades. Abstracts can be used to identify changes in practice, to pinpoint the timing of scientific breakthroughs, and provide a network analysis of authors.

Dataset Description (pdf) | Sample Dataset (pdf) | Sample Dataset (accdb) | Sample Dataset (csv) | Meeting Abstract Description Package (zip)

Quality Oncology Practice Initiative (QOPI)

QOPI is an oncologist-led, practice-based quality assessment program designed to promote excellence in cancer care by helping practices create a culture of self-examination and improvement. QOPI provides a standard methodology, robust library of quality metrics for oncology, and a collection tool to reliably and routinely assess care, inform quality improvement activities, and demonstrate quality to patients and external stakeholders. Practices participate in manual abstraction onto the secure web-based platform twice per year. For more detailed information about QOPI, please visit ASCO Practice Central.

Steps for Obtaining ASCO Information for Research

The following process should be followed for requests of ASCO datasets, except QOPI dataset.

Step 1: Submit Request

- Complete the Research Project Proposal Application

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER