FRIENDS of CANCER RESEARCH

# Multi-Regional Clinical Trials: Addressing Standard of Care Variability

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## Executive Summary

Global multi-regional clinical trials (MRCTs) in oncology accelerate access to new therapies, improve the diversity and generalizability of clinical data, and enable more efficient regulatory review across regions. A central challenge in MRCT design is selecting an appropriate standard of care (SOC) comparator, which anchors interpretation of a new therapy's efficacy and safety relative to existing treatments. SOC can vary widely across regions due to differences in regulatory approvals, clinical guidelines, real-world practice, access, and reimbursement. It is often not a single treatment but a range of acceptable, context-dependent options that evolves over time as new evidence emerges, presenting two key challenges for trial design: (1) SOC may shift during an ongoing trial and (2) multiple SOCs may exist simultaneously, complicating selection of a single comparator.

Beyond scientific complexity, comparator selection raises ethical and operational considerations. Patients and investigators must view the control arm as acceptable and relevant to current practice; otherwise, trials risk poor enrollment or high dropout rates. Trial sponsors must therefore take a thoughtful approach to comparator selection that balances scientific rigor, ethical integrity, and global feasibility. Friends of Cancer Research (*Friends*) convened a multi-stakeholder working group including experts from the U.S. Food and Drug Administration (FDA), pharmaceutical companies, academia, and patient advocacy to identify key considerations and potential strategies for selecting and justifying comparators in oncology MRCTs.

Key Considerations:

- Comparator arms should reflect clinically meaningful standards and not be inferior to therapies demonstrating clinical benefit.
- Strategy for comparator selection and design should evaluate possible SOC evolution during trial planning and conduct.
- Factors such as regulatory approvals, clinical guidelines, real-world use, feasibility, reimbursement, and patient and clinician preferences should all be considered.
- Balancing regional applicability, particularly in the U.S., with global feasibility is crucial, as SOC in one region may not be approved or practical in others.

Strategic Approaches:

- Predefine acceptable options (e.g., investigator's choice or regional controls) when multiple SOCs exist.
- Anticipate SOC changes as much as possible and pre-specify limited design adaptations or supplementary cohorts if needed.
- Use descriptive analyses, embedded cohorts, or real-world data (RWD) to contextualize findings when new SOCs emerge mid-trial.
- Document comparator rationale and engage early with regulators to ensure scientific and ethical acceptability.

This white paper outlines considerations to guide trial sponsors, from defining the patient population and SOC options to evaluating feasibility, ethics, timing risks, and regulatory input throughout the process. These are not intended as a strict roadmap but as flexible considerations to support alignment and transparency in MRCT design. While perfect solutions may not be attainable, a thoughtful and ongoing process can improve applicability and transparency in comparator selection, ensuring trials remain feasible, meaningful, and representative across regions.

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This white paper was developed through discussions that included these experts and other perspectives representing academia, industry, the U.S. Food and Drug Administration, and the patient advocacy community. The views expressed here represent the collective insights from working group discussions and do not necessarily reflect the official positions of any individual organization.

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## Introduction

Global multi-regional clinical trials (MRCTs) in oncology drug development are commonly used to support marketing applications across multiple regulatory jurisdictions. Studying new medicines and regimens in MRCTs has the potential to improve the generalizability of results, accelerate global drug development, and support more efficient regulatory review. Both the International Council for Harmonisation (ICH) E17 guideline and the U.S. Food and Drug Administration's (FDA) guidance on clinical evidence generation from oncology MRCTs underscore the value of MRCTs in establishing efficacy and safety across diverse patient populations and geographic regions.[1,2]

Selecting an appropriate comparator arm remains one of the most challenging aspects of MRCT design. Standards of care (SOC) can vary significantly across and within regions due to differences in regulatory approvals, clinical guidelines, real-world practice, access, and reimbursement. In some settings, more than one regimen may reasonably be considered SOC, with 'gray zones' that reflect the realities of clinical decision-making for individual patients. Additionally, the therapies most used in practice may differ from those formally approved by regulatory agencies or recommended in clinical guidelines, particularly when access, reimbursement, or tolerability influence real-world uptake. In the context of clinical trial design and conduct, challenges in comparator selection generally reduce to two core issues: (1) the timing of new SOC adoption relative to an ongoing trial, and (2) the presence of multiple SOC options during trial conduct.

These challenges have far-reaching implications. Comparator selection is not only a scientific or regulatory issue, but also a patient-centered, ethical, and practical one, as trial credibility and feasibility ultimately rests on whether patients and their treating physicians view the comparator as acceptable and relevant to their treatment. A comparator must maintain clinical equipoise and be one that patients are willing to receive when randomized; otherwise, trials risk poor enrollment, high dropout rates, or ultimately becoming infeasible to enroll.[3] Comparator regimens should also allow for clear isolation of the contribution of phases and/or new products in investigational regimens that have multiple phases of treatment and/or combinations of products across one or more treatment phases (e.g., combination regimens with both neoadjuvant and adjuvant phases). Regulators have increasingly emphasized that control regimens should be therapies demonstrating substantial clinical benefit, even when access may be regionally delayed. Comparator selection directly affects the feasibility, ethical integrity, and interpretability of global oncology trials.

Without workable solutions to address SOC variability, some global MRCTs may not be pursued at all — limiting opportunities for patients to access novel therapeutics and for researchers to generate robust evidence across diverse populations. In other cases, trials may proceed but be highly impacted by skewed regional representation, which increasingly shapes submission and registration discussions. This reality underscores both the urgency of the problem and the need for predictable pathways to guide comparator selection across evolving SOC landscapes.

## Scope

This white paper focuses on comparator regimen selection in MRCTs, with an emphasis on oncology trials intended to support marketing applications in the U.S. that also enable ex-U.S. regulatory submissions. A related consideration is the expectation from many health authorities for sufficient representation of

patients from their own regions. While this intersects with comparator selection, it is not the primary focus of this paper.

Building on existing regulatory guidance, this paper expands on high-level principles by: (1) outlining key considerations for defining and justifying SOC control arm selection in a global context, (2) presenting archetypes and scenarios that illustrate common timing and multiplicity challenges, (3) exploring design strategies and solutions to support more predictable and feasible trial planning, and (4) proposing a framework and future directions for advancing regulatory and operational approaches.

## Understanding and Defining Standard of Care

SOC in oncology is inherently dynamic and context dependent. Rather than a single, universally accepted regimen, SOC often spans a range of options shaped by cancer types, labeled indications, clinical guidelines, real-world uptake, patient preferences, and the practical realities of access, reimbursement, and deliverability (e.g., chimeric antigen receptor T-Cell [CAR T] or radiopharmaceutical therapies). In MRCTs, these elements are magnified by the often lengthy timelines of oncology trials, during which the treatment landscape can shift in variable and sometimes dramatic ways across regions. While not all disease areas face this challenge equally, the issue is especially pronounced in fields with rapidly evolving SOCs, where new approvals or data readouts can redefine practice within the timespan of a clinical trial. Changes to a comparator arm mid-trial are operationally challenging and highly impracticable to implement, and shifts in the landscape can impact clinical equipoise, undermine enrollment, create heterogeneity, or render results less interpretable to regulators and clinicians.

Because SOC cannot always be clearly established as a single entity, especially in fields such as oncology where multiple therapies may exist or SOCs are rapidly evolving, patient experience and acceptability should remain central. What matters is not only what is regulatory approved or guideline-recommended, but whether patients and clinicians view the treatment as acceptable and relevant, in both routine care and the context of a clinical trial, given toxicity, convenience, and perceived benefit.

## Appraising Comparator Options in a Changing Landscape

Sponsors must continuously track multiple factors when selecting a global control arm—a task made harder when the landscape is evolving rapidly or a new therapy may offer transformational benefit. Key factors include:

- Recent and near-term regulatory approvals, including specific labeling language for the intended population and line of therapy
- Variation in timelines for global approvals for emerging new treatments
- Clinical guideline recommendations (e.g., NCCN, ESMO) and their evidentiary strength
- Patient and clinician preferences as reflected in routine clinical practice
- Real-world uptake (if available) and typical or shifts to treatment sequencing
- Feasibility of delivery, including sourcing, site capabilities, and infrastructure requirements, especially for emerging treatment options requiring specific site expertise
- Reimbursement and access (coverage, formulary status, logistics)

It is also important to distinguish the types of limitations that may arise when evaluating comparator options. A regimen may be infeasible when it cannot realistically be delivered within the study framework due to regulatory, ethical, or logistical barriers. It may be impractical when it is technically possible but requires disproportionate operational or infrastructure investment. Such limitations may also restrict the number and types of sites that can participate, potentially narrowing patient diversity and reducing the generalizability of results to the broader population for which the drug is intended. In some circumstances, a regimen may become unacceptable when clinical equipoise no longer exists, such as when a therapy with superior benefit has entered clinical practice. Clarifying these distinctions can help align discussions of feasibility and appropriateness across regions.

Regulators have emphasized that selecting a less-active comparator, or a less-commonly-used comparator, risks undermining trial credibility if it appears designed to exaggerate the investigational therapy's benefit. When appraising the evidentiary foundation, considerations include the approval type (e.g., traditional vs. accelerated), the magnitude and consistency of benefit (including potential class effects), study design (e.g., head-to-head vs. add-on design), the associated risks (e.g., safety, tolerability, convenience of administration), and the maturity and nature of endpoint data (e.g., overall survival [OS] vs. intermediate or surrogate endpoints). However, the more practical test is whether the chosen comparator can credibly serve as SOC for the intended population such that the comparator regimen is acceptable to patients and investigators.

## Considerations in Assessing Global Trial Applicability

Recent FDA deliberations have highlighted how comparator choice can directly influence regional enrollment and, ultimately, regulatory interpretation. In one recent oncology MRCT, the selected control arm may have contributed to limited U.S. enrollment and raised questions about the applicability of results to the U.S. population. Despite meeting its primary endpoint, the resulting imbalance and inconsistent effects across regional subgroups led the advisory committee to conclude that the results were not sufficiently applicable to the U.S. patient population.[4] This example illustrates how a comparator that is scientifically reasonable but misaligned with regional practice can inadvertently limit participation and undermine applicability in key regions.

U.S. law requires that new drug approvals be supported by substantial evidence of effectiveness from adequate and well-controlled investigations and sufficient evidence to establish safety under the proposed conditions of use.[5] The statute and associated regulations do not mandate that such evidence be generated exclusively in U.S. patients, but the expectation is that trial data must be applicable to the intended patient population.

In practice, FDA has increasingly emphasized the importance of U.S. applicability—both to ensure that control arms remain relevant to current U.S. practice and to provide confidence that safety signals are adequately characterized in U.S. patients. This emphasis reflects concerns about population differences, evolving SOCs, and trial credibility, but it has also created uncertainty for sponsors when global feasibility is at odds with regional expectations.

## Feasibility and Applicability Tension

A central challenge in MRCT comparator selection is balancing regional applicability (particularly in the U.S.) with global feasibility. For sponsors, approval in the U.S. is often a primary objective, and FDA expects trials

to include controls aligned with U.S. practice (Table 1). Yet most new regimens are not globally approved, consistently reimbursed, or delivered quickly enough across regions to serve as immediate global control arms, creating feasibility and operational barriers when considering study designs with a single comparator.

This tension is operational as well as regulatory: supplying control arm therapies globally, variability in site capabilities, and infrastructure gaps (e.g., with administration of CAR-T or radioligands) can make otherwise appropriate SOCs impractical to implement. Moreover, every additional comparator option or adaptation layer, including expanding control arm options using investigator's choice, adds extra statistical and regulatory risk.

Comparator selection often requires balancing scientific rigor, regional applicability, and global feasibility, recognizing that no single approach may suffice across all trials.

Table 1. Considerations and Practical Challenges in Comparator Selection

| Considerations | Practical Challenges |
|---|---|
| Applicability of trial results to current SOC may become a review consideration if available therapies evolve during the study | Prolonged trial timelines mean comparators may become outdated mid-study, creating uncertainty for both design and interpretability. |
| New SOC is not globally available | Global differences in approval, reimbursement, and access make it difficult to ensure uniform delivery of the control therapy across regions. Sponsors must balance designing a trial that reflects regional SOC while maintaining interpretability of pooled results. In some cases, new approvals are limited to specific subpopulations, creating misalignment in what constitutes SOC for the broader disease population. |
| Trial control arms should not be *a priori* inferior when new therapies demonstrate clinical benefit | Determining what constitutes a substantial benefit and weighing the endpoint used may rely on cross-trial comparisons and can be subjective; implementing changes when the trial is still ongoing (either accruing or awaiting primary endpoint maturity) may be impracticable due to operational complexity, disruption of enrollment, and risks to the prespecified analysis plan. |
| Adaptation may be expected (e.g., investigator's choice, updated control, refinement of patient subgroups, regional applicability data) depending on approval of new therapy | Careful planning at trial design and initiation to allow for adaptations, but still requires protocol amendments, additional cohorts, reconsenting, and/or new studies, which can complicate interpretation, increase time and cost, and reduce the credibility of pooled analyses. |

## Archetype Scenarios

Recent experience shows how rapidly oncology SOC can evolve. For example, when KRAS G12C inhibitors were approved and became available for patients with KRAS-mutated non-small cell lung cancer, many eligible patients transitioned to these targeted therapies, affecting enrollment and the feasibility of ongoing trials that used chemotherapy-based control arms.[6] Similarly, the introduction of antibody–drug conjugates in HER2-positive breast cancer reshaped expectations for control arms within only a few years. These examples highlight the need to design MRCTs that remain interpretable and feasible even as the treatment landscape shifts.

Comparator challenges often reflect three interacting dimensions:

1. The timing of SOC change relative to an ongoing trial,
2. The magnitude and scope of the new therapy's clinical benefit, including the maturity of evidence, and
3. The resulting impact on feasibility, equipoise, and interpretability.

While adaptability remains an important design consideration, substantial protocol modifications during trial conduct are impracticable. Once initiated, trials are generally intended to answer a defined scientific question using a prespecified design. Therefore, when new therapies emerge mid-study, emphasis should be placed on preserving interpretability and contextualizing findings. In these circumstances, a totality of evidence of approach leveraging complementary data sources or analyses may be used to provide additional context and reinforce confidence at the time of readout, ensuring that results remain informative in light of evolving SOC.

The following scenarios illustrate common situations sponsors may encounter. This list is not exhaustive but reflects frequently observed cases where SOC heterogeneity complicates comparator selection.

## Timing and Magnitude of SOC Change

### Pending Change to SOC Before Trial Initiation

*A near-term transformative approval is anticipated before or during trial initiation.*

Implication: Sponsors must assess whether the planned comparator will remain credible once enrollment begins and consider pre-specifying contingency strategies. Early regulatory dialogue regarding potential contingency approaches and the acceptability of the planned comparator is important if approval appears imminent.

### Transformative Therapy Emerges Mid-Trial

*A new therapy demonstrating substantial OS improvement, cleaner safety profile, or simpler administration (e.g., PD-(L)1 inhibitors, KRAS G12C inhibitors, next-generation antibody-drug conjugates [ADC]) becomes available and rapidly adopted in some regions or within specific patient subgroups.*

Implication: Comparator relevance may erode mid-study; whether adaptation is practicable depends on the stage of enrollment, feasibility of protocol changes, and whether the new indication overlaps with the enrolled population. Ethical and clinical pressure for crossover can increase, while enrollment may slow in regions where the new therapy is accessible. Differences in uptake across regions may also introduce heterogeneity and confound OS analyses due to varying subsequent therapy use.

### Late shift in SOC During On-Going Trial

*A new therapy is approved close to database lock or after primary analysis.*

Implication: Late shifts are typically less disruptive operationally but may affect interpretability, labeling discussions, and the perceived relevance of results in light of current practice.

### Incremental Therapy Enters the Landscape

*A new regimen offering modest incremental benefit (e.g., small progression-free survival [PFS] gain or an add-on to existing therapy) becomes available.*

Implication: Ethical equipoise generally remains, so comparator changes are often unnecessary once enrollment has begun. However, varying regional adoption can influence accrual and introduce modest heterogeneity, particularly if the add-on becomes common in some markets but not others.

### Multiplicity of SOC Options

Multiplicity challenges can arise when several regimens or combination backbones are considered standard across or within regions. In oncology, many MRCTs use an add-on design (investigational product + SOC vs. SOC alone), where the key question is which SOC backbone(s) to include globally. These differences often reflect entrenched regional practice patterns or reimbursement structures rather than recent temporal shifts. Sponsors must balance scientific rigor, feasibility, and interpretability when determining whether to use a unified global backbone or permit regional variation.

#### Multiple Comparators with Similar Efficacy

*Situations where more than one regimen may reasonably be considered SOC because therapies provide modest and comparable benefit to each other. This occurs frequently in later-line settings but can also arise in earlier lines, particularly in diseases with multiple approved options or combinations.*

Implication: Investigator's choice may be feasible if options are functionally equivalent, though heterogeneous trial results can complicate regulatory interpretation and labeling.

#### Regional Asymmetry in Access or Approvals

*A therapy is approved in one or a limited set of regions.*

Implication: Sponsors must weigh whether to exclude certain regions, supply therapy where it is not yet available but acceptable to local health authorities, or conduct parallel or bridging studies. Regulators have signaled that lack of access in a given geography is not, on its own, sufficient justification for continuing an outdated comparator.

### Additional Feasibility Considerations

Infrastructure, reimbursement, or site capability differences can also affect the feasibility of implementing certain therapies as control arms. While such cases may be uncommon, complex modalities like CAR T or radioligand therapies can illustrate how practical delivery barriers may limit their inclusion as a comparator in multi-regional settings. Anticipating these constraints early and addressing them in regional planning and comparator justification can help maintain both trial feasibility and applicability.

## Design and Analytical Approaches for Maintaining Trial Applicability

Approaches to selecting and designing comparator arms in MRCTs each have distinct advantages, limitations, and feasibility implications (Table 2). While numerous statistical and methodological approaches exist, regulators have emphasized that their acceptability depends on context and cannot be assumed. This section outlines general principles and design options that can help maintain interpretability and relevance when standards of care evolve.

### General Principles

#### Scientific Rigor and Trial Integrity

- Retain randomized controlled comparisons as the foundation wherever feasible.

- Consider both the magnitude and maturity of benefit when assessing whether a comparator remains appropriate (e.g., whether a PFS advantage alone is sufficient or whether OS evidence is required).
- Statistical or adaptive methods (e.g., Bayesian framework to address treatment effect heterogeneity or Sequential Multiple Assignment Randomized Trial [SMART] designs for multiple response-based treatment paths) may help address heterogeneity, but they cannot substitute for comparators that are no longer aligned with current practice.

## Patient and Ethical Acceptability

- Prioritize comparators that maintain clinical equipoise and patient acceptability.
- Enrollment feasibility is a practical test of SOC acceptability.

## Planning for Change and Contextualizing Evidence

- Sponsors can preemptively assess the likelihood, timing, and operational implications of an SOC change, evaluating whether anticipated shifts are imminent, regionally staggered, or likely to affect enrollment and interpretability, and align these assessments with pre-specified contingency strategies (e.g., sensitivity analyses, dual primary endpoints, bridging cohorts, or exploratory analyses among patients enrolled after a new SOC emerges).
- In practice, the feasibility of completing trial enrollment may serve as an important indicator of whether the selected comparator remains acceptable. If a study is able to enroll as planned despite the introduction of a new SOC, this may signify that the trial's comparator was appropriate and that the design continues to reflect a relevant clinical context. Conversely, significant enrollment challenges may signal that the prevailing treatment landscape has shifted and should prompt re-evaluation through discussion with regulatory authorities.
- When SOC evolves during the trial, focus on augmenting the totality of evidence. Options include:
    - Supplementary clinical trial data or RWD.
    - to benchmark outcomes under the new SOC.
    - Embedded or regional cohorts that reflect updated clinical practice without undermining the primary analysis.
    - Post hoc or sensitivity analyses to test robustness of outcomes in subgroups defined by enrollment timing or geography.
    - Ensure that the overall data package, including randomized, supplemental, and contextual data, collectively supports interpretability and relevance to current clinical practice.

Early regulatory dialogue can help align on labeling expectations and contextual analyses that may be needed if SOC evolves.

## Table 2. Approaches to Maintain Trial Applicability Under Evolving Standards of Care

| Approach | When it May Fit | Advantages | Risks / Limitations |
|---|---|---|---|
| **Design Strategies for Prospective Flexibility** | | | |
| Investigator's Choice | Settings where multiple options provide modest and comparable benefit | Reflects real-world practice; endpoints remain interpretable if options are functionally equivalent; may reduce patient dropout from control arm | Unpredictable and uneven enrollment to each option; alignment on what constitutes functional equivalence can be difficult—differences in outcomes (e.g., OS vs. PFS benefit), safety profiles, or evidence maturity across the selected options may complicate labeling and regulatory interpretation |
| Region-specific controls | Regional asymmetry in approvals/access | Addresses local feasibility; ensures relevance to local regulators | Adds complexity for implementation if controls require different schedules and/or management, which can make blinding difficult; risks underpowered subgroups unless accrual is prespecified for each subgroup; complicates pooled analysis for overall trial effect; may not be possible due to regional implementation differences |
| Planned design adaptations | When a SOC change may occur during the trial and can be anticipated and pre-specified in advance | Allows prospectively defined changes (e.g., adaptation to a new comparator, adding an arm, modifying stratification) without undermining trial integrity and statistical validity | Operationally burdensome; requires extensive upfront planning, statistical adjustments, and regulatory dialogue; flexibility may be limited if changes occur earlier or later than anticipated |
| **Contextual Evidence Additions During or Post-Trial** | | | |
| Embedded cohort | When a SOC change is anticipated during the study period, but a full redesign is not feasible | Preserves the original trial design and analysis plan while allowing collection of comparator data aligned with the new SOC in selected regions; provides context without undermining the primary evidence | Operationally complex (requires protocol amendments, site-level variation, and careful delineation of how supportive vs. primary evidence will be used); may introduce heterogeneity that complicates interpretation |
| Supplemental bridging or U.S. specific cohorts | U.S. SOC diverges from global practice | Ensures U.S. applicability; maintains global enrollment | Added trial burden; feasibility may be limited if U.S. enrollment is already lagging; data may be viewed as less robust than fully integrated design |

| Approach | When it May Fit | Advantages | Risks / Limitations |
|---|---|---|---|
| Alternative or Complementary Evidence Generation | | | |
| Parallel region-specific trials | Rare populations where U.S. comparator feasibility is limited | Allows collection of U.S.-specific data while leveraging global enrollment for confirmatory endpoints | Limited regulatory precedent; risk of non-acceptance if one trial is conducted entirely ex-U.S.; potential heterogeneity in the patient cohorts, and endpoints |
| External Clinical Data | When comparator delivery is impractical | Provides supportive context; may reassure regulators/ clinicians | Not central to inference; limited regulatory precedent; potential bias; potentially greater heterogeneity in collection outcome data |
| Staggered or phased enrollment | When feasibility differs across regions or SOC is evolving in some geographies | Allows enrollment to proceed where feasible; provides flexibility to incorporate new comparators as standards evolve | Slower global enrollment; may create regional imbalances; could complicate pooled analysis and regulatory interpretation due to non-simultaneous accrual |

## Guided Approach to Comparator Selection

Comparator selection benefits from a structured, transparent process that progressively filters the broad landscape of potential SOCs into a justified, feasible choice. A "funnel" approach can help sponsors document rationale and demonstrate interpretability and applicability for regulators. Comparator discussions are best addressed during the pre-phase 3 meeting, when trial design and comparator decisions can still be meaningfully influenced. Once a study is underway, implementing mid-trial changes to the comparator is rarely feasible—protocol amendments can take six months to a year to operationalize across global sites. Early dialogue at this stage helps ensure that the planned comparator and contingency strategies remain acceptable, reducing the need for disruptive mid-trial modifications.

Proposed Steps:

1. Clarify the target setting: Review disease, line of therapy, key jurisdictions, and trial purpose.
2. Identify plausible SOC options: Consider regulatory approvals, guidelines, real-world practice, access, delivery feasibility, and evidentiary maturity (e.g., whether benefit is supported by PFS alone or requires OS evidence).
3. Screen for feasibility and ethical acceptability: Exclude options that are undeliverable (infeasible), impose undue logistical or operational burden (impractical), or ethically inappropriate (unacceptable).
4. Prioritize applicability: Ensure comparator(s) and planned enrollment align with key regions while considering global feasibility.
5. Assess timing and adaptation risks: Evaluate likelihood of SOC changes during the trial; pre-specify mitigation (e.g., sensitivity analyses, planned redesign, supplementary cohorts, dual primary endpoints, regional subgroup data).
6. Engage regulators at early key milestones: Seek early and structured input on comparator justification, particularly before protocol finalization or if major SOC shifts occur.
7. Reassess periodically: Review accrual patterns, regional uptake, and emerging SOC shifts during conduct to determine whether contextual or supplementary data will be needed to support interpretability.

This process provides a common framework to ensure comparator selection remains scientifically justified, ethically sound, and operationally feasible, while supporting transparency and consistent dialogue across sponsors, regulators and patients.

## Future Directions

The working group acknowledged that there are no universally applicable solutions for comparator selection in MRCTs. The challenges created by evolving and heterogeneous SOCs are unlikely to be resolved by a single approach, and sponsors, regulators, and other stakeholders will need to pressure test a range of strategies to identify workable paths forward. A shift toward totality-of-evidence approaches that integrate prospective trial data with contextual external data or descriptive analyses may offer a practical way to address evolving SOC landscapes without undermining the core trial design.

A potential roadmap could include:

- Clearer articulation on how to balance regulatory requirements with practical expectations for applicability and safety would help sponsors design trials with greater predictability. Opportunities may include enhanced guidance or early, multi-agency dialogue to clarify when global evidence is sufficient and when U.S.-specific enrollment or comparators are essential.
- Use of retrospective data or prospective simulation exercises to test how different design and analysis strategies (e.g., investigator's choice, trial-within-a-trial, bridging cohorts) would perform under real-world SOC shifts.
- Convene sponsors, regulators, clinicians, and patients to assess feasibility and acceptability of different approaches, including trade-offs between scientific rigor, operational burden, and patient relevance.
- Implement statistical and design strategies to strengthen interpretability when heterogeneity cannot be fully avoided.
- Layout considerations around issues such as endpoint maturity (e.g., whether PFS alone is sufficient to redefine SOC), acceptable use of bridging data, and how much regional asymmetry can be tolerated.
- Explore models for multi-agency or joint regulatory engagement to enable earlier, more consistent feedback on comparator strategy in MRCTs (e.g., expanding components of Project Orbis to occur during clinical development phase).

Several open questions remain for the field:

- What magnitude and type of benefit should trigger reconsideration of a control regimen — is a PFS improvement sufficient, or should OS or long-term data be required?
- How can patient perspectives on acceptability and willingness to enroll be more systematically integrated into comparator selection?
- How far into trial enrollment or endpoint maturity is it reasonable to adapt a comparator strategy, and what are the implications for analysis integrity?
- How can trials balance the need for region applicability (particularly U.S. applicability) with the operational feasibility of enrolling patients in regions where new SOCs are not yet approved or reimbursed?
- How much heterogeneity can be accommodated without undermining interpretability and labeling?
- Under what circumstances can external controls or RWD provide meaningful supplemental support when SOC shifts post-initiation?

Developing answers to these questions will require structured experimentation, ongoing dialogue, and shared learning across stakeholders. While perfect solutions may not be attainable, a deliberate process to evaluate and refine strategies can bring greater predictability and transparency to comparator selection in MRCTs, ultimately ensuring that trials remain both feasible and relevant to patients.

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