# Global Trials, Local Relevance: A Scientific and Regulatory Framework for Regional Enrollment in Cancer Drug Development

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## ABSTRACT

**PURPOSE** Global oncology trials face increasing scrutiny over regional enrollment imbalances, as regulatory agencies such as the US Food and Drug Administration, European Medicines Agency, and Pharmaceuticals and Medical Devices Agency demand data reflective of population diversity. This push is grounded in evidence that genetic polymorphisms (eg, *UGT1A1*28*, *CYP2D6*), human leukocyte antigen–related toxicities, and biomarker prevalence (eg, epidermal growth factor receptor  mutations in approximately 15% of Western *v* approximately 50% of Asian patients with lung cancer) can significantly influence treatment outcomes.

**METHODS** We reviewed scientific literature, regulatory case studies, and methodological innovations addressing regional heterogeneity in oncology trials. Particular focus was given to statistical tools such as adaptive randomization for real-time enrollment balancing, Bayesian hierarchical models for data borrowing across regions, and Multi-Regional Clinical Trial designs for structured consistency assessments. Control arm variability because of regional differences in standard of care and drug access was also examined.

**RESULTS** Recent regulatory setbacks, especially involving Asia-centric trials, underscore the consequences of insufficient regional planning. Emerging statistical approaches, including adaptive and Bayesian methods, show promise in managing heterogeneity while preserving trial integrity. Persistent challenges include disparities in trial infrastructure, molecular subtype distributions, and comorbidity patterns. Broader regional inclusion and integration of real-world evidence are increasingly critical to overcoming these limitations.

**CONCLUSION** Regional enrollment should be viewed not as a regulatory formality, but as a scientific and ethical priority. The future of global oncology trials hinges on proactive regional planning, innovative methodology, and cross-sector collaboration. Aligning global efficiency with local relevance can enhance scientific robustness, support regulatory alignment, and expand equitable access to novel cancer therapies worldwide.

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## INTRODUCTION

"*A rising tide lifts all boats.*"

President John F. Kennedy

The globalization of cancer clinical trials has fundamentally transformed oncology drug development, enabling faster patient accrual and broader representation across heterogeneous populations.[1] However, this expansion has raised critical questions about the transportability of clinical trial results across different regions and populations.[2] As regulatory agencies increasingly scrutinize regional enrollment patterns and outcomes, the oncology community must thoughtfully address how to design trials that generate globally relevant evidence while meeting local regulatory expectations.[3]

This commentary examines the multifaceted challenges and opportunities of regional enrollment in cancer registrational trials. We explore the scientific rationale underlying regional

representation requirements, evaluate data transportability across populations, and analyze regulatory perspectives from major agencies. The article addresses the complex challenge of managing different standards of care across regions and presents innovative statistical approaches that balance global efficiency with regional relevance.

These reflections are further provoked by the unprecedented pressures of trial timelines, complexity, and geographic concentration, which are examined in greater detail below. Our goal is to provide actionable guidance for clinical development teams in challenging times and to move the field beyond viewing regional enrollment as merely a regulatory hurdle, toward embracing it as a scientific opportunity to generate more robust evidence for patients with cancer worldwide.

## THE STRATEGIC IMPORTANCE OF REGIONAL ENROLLMENT

### Regulatory Landscape and Market Access

Regional enrollment considerations have become paramount in cancer registrational trials for several compelling reasons. First, major regulatory agencies including the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and Pharmaceuticals and Medical Devices Agency (PMDA) have established expectations for adequate regional representation to support local marketing applications. The FDA's guidance on ethnic factors in drug development and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E5 guideline emphasize that foreign clinical data should be relevant to the target population, requiring demonstration that ethnic factors do not significantly affect drug safety or efficacy.[4]

From a market access perspective, regional enrollment directly influences reimbursement decisions. Health technology assessment bodies increasingly demand local evidence to inform coverage determinations, particularly for high-cost oncology therapeutics. Countries such as Germany (IQWiG), the United Kingdom (NICE), and Canada (CADTH) often prioritize studies that include patients from their health care systems when evaluating clinical and economic value.[5]

The growing significance of these considerations is aptly demonstrated by the widely reported May 2025 vote of the FDA Oncologic Drugs Advisory Committee on Glofitamab, when it ruled against the applicability of the patient population and results from the phase III STARGLO trial to the US population of patients with relapsed/refractory diffuse large B-cell lymphoma, in which 48% of patients were enrolled in Asian regions, against 9% in the United States. This follows a 2022 review by the same FDA committee of the ORIENT-11 trial of sintilimab for metastatic non–small cell lung cancer, conducted exclusively in China, which was already the subject of a FDA staff report's conclusion that the data used to back the marketing application did not meet criteria required for US approval. Although the pressures to identify fresh populations for trials continue to drive the exploration of new avenues, the growing number of oncology development programs based solely or predominantly on clinical data from China—and the regulatory problems they encounter—call into question the value of trials that fail to take adequate account of the need for a strategy balancing regional relevance with global efficiency.[6,7]

### Scientific Rationale for Regional Representation

Beyond regulatory requirements, compelling scientific principles support approaches that appropriately incorporate regional enrollment into development strategies. Cancer biology, while sharing fundamental characteristics globally, exhibits important regional variations that can significantly affect therapeutic outcomes.

#### *Genetic Polymorphisms and Drug Metabolism*

Population genetics research has revealed substantial regional variation in drug-metabolizing enzymes that directly affect oncology treatment outcomes. For example, *UGT1A1*28* polymorphisms, which affect irinotecan metabolism, occur in approximately 10% of Caucasians but are much rarer in Asian populations. This difference has led to different dosing recommendations for irinotecan-containing regimens across regions. Similarly, *CYP2D6* polymorphisms affecting tamoxifen metabolism show marked geographic variation, with implications for endocrine therapy efficacy in breast cancer.[8]

#### *Human Leukocyte Antigen Associations and Immune-Related Toxicities*

Human leukocyte antigen (HLA) allele frequencies vary dramatically across populations and can predict severe immune-related adverse events. The strong association between *HLA-B*5701* and abacavir hypersensitivity, although not directly oncology-related, demonstrates how genetic variation can affect drug safety. In oncology, emerging evidence suggests HLA associations with immune checkpoint inhibitor toxicities may vary by population, potentially affecting the benefit-risk profile of immunotherapies across regions.[9]

#### *Biomarker Prevalence and Cancer Subtypes*

Multiple examples demonstrate regional variation in cancer-driving mutations and biomarkers. Epidermal growth factor receptor mutations in non–small cell lung cancer occur in 10%-15% of Western patients but 40%-60% of East Asian patients, fundamentally altering treatment algorithms. *KRAS G12C* mutations show different prevalence patterns across ethnicities, affecting eligibility for targeted

therapies such as sotorasib. *ALK* rearrangements also demonstrate regional variation, with higher frequencies observed in Asian nonsmokers.[10]

### *Environmental and Lifestyle Factors*

Regional differences in environmental exposures, dietary patterns, and lifestyle factors can influence cancer biology and treatment response. Hepatitis B coinfection rates vary dramatically by geographic region, affecting both liver cancer incidence and the safety profile of systemic therapies that may cause hepatitis B reactivation. Aflatoxin exposure patterns influence hepatocellular carcinoma molecular subtypes, potentially affecting targeted therapy responses.[11]

### *Body Composition and Pharmacokinetics*

Regional differences in body composition, particularly muscle mass and fat distribution, can affect drug pharmacokinetics and dosing strategies. Asian populations often have different body surface area distributions and lean body mass percentages compared with Western populations, which may influence dosing of cytotoxic chemotherapies traditionally dosed by body surface area.[12]

### *Concurrent Medications and Drug Interactions*

Regional variation in concurrent medication use, including traditional medicines, can significantly affect drug-drug interactions and safety profiles. Traditional Chinese medicine use is common in Asian populations and may interact with modern oncology therapeutics. Similarly, regional differences in supportive care medications, anticoagulation strategies, and management of comorbidities can affect both safety and efficacy outcomes.[13]

### *Infectious Disease Comorbidities*

Regional variation in infectious disease prevalence can significantly affect oncology treatment safety and efficacy. Tuberculosis reactivation risk with immunosuppressive therapies varies dramatically by geographic region. Hepatitis C coinfection rates affect both drug selection and monitoring strategies. These factors are particularly important for immune checkpoint inhibitors and cellular therapies that can reactivate latent infections.[14]

### *Cancer Care Infrastructure and Treatment Delivery*

Regional differences in health care infrastructure can affect treatment delivery and outcomes in ways that affect trial interpretation. Variation in radiation therapy techniques, surgical approaches, and supportive care capabilities across regions may influence both control arm performance and experimental treatment effects. These differences can be particularly pronounced between developed and emerging markets.[15]

### *Resistance Patterns and Previous Therapies*

Regional differences in treatment access and sequencing can lead to different resistance patterns that affect subsequent therapy effectiveness. For example, previous CDK4/6 inhibitor exposure in metastatic breast cancer varies significantly by region because of reimbursement differences, potentially affecting responses to subsequent therapies in clinical trials.

Treatment paradigms also differ substantially across regions, influencing control arm selection and comparative effectiveness. Standard-of-care variations—whether due to drug availability, clinical guidelines, or health care infrastructure—can affect trial interpretation and regulatory acceptance.[16]

Diversifying regional enrollment is not just a scientific imperative—it is a hedge against trial delays, regulatory friction, and recruitment failure. By reducing reliance on saturated geographies, sponsors can avoid bottlenecks, reduce time to enrollment, and build trials that are more representative and ethically sustainable—on condition that the resulting study population will prove to be a valid representation of the target population for the intended treatment (Fig 1 and Table 1).

## STRATIFICATION STRATEGIES FOR REGIONAL OUTCOME ANALYSIS

### Statistical Approaches to Regional Analysis

Effective stratification of patient outcomes on the basis of regional enrollment requires sophisticated statistical planning and analysis strategies. The key is to balance the need for regional insights with overall trial power and interpretability.

Prospective regional stratification should be built into randomization schemes, ensuring balanced treatment allocation within major geographic regions. This approach enables meaningful regional subgroup analyses while maintaining overall trial integrity.

Hierarchical modeling approaches can leverage the natural clustering of patients within regions, borrowing strength across similar health care systems while accounting for regional heterogeneity. Bayesian hierarchical models are particularly useful for this purpose, allowing for region-specific effect estimates while stabilizing estimates through partial pooling.

Interaction testing frameworks should formally evaluate treatment-by-region interactions, using appropriate multiple testing adjustments. Prespecified interaction thresholds (eg, CI approaches) can guide interpretation of regional consistency.[17]

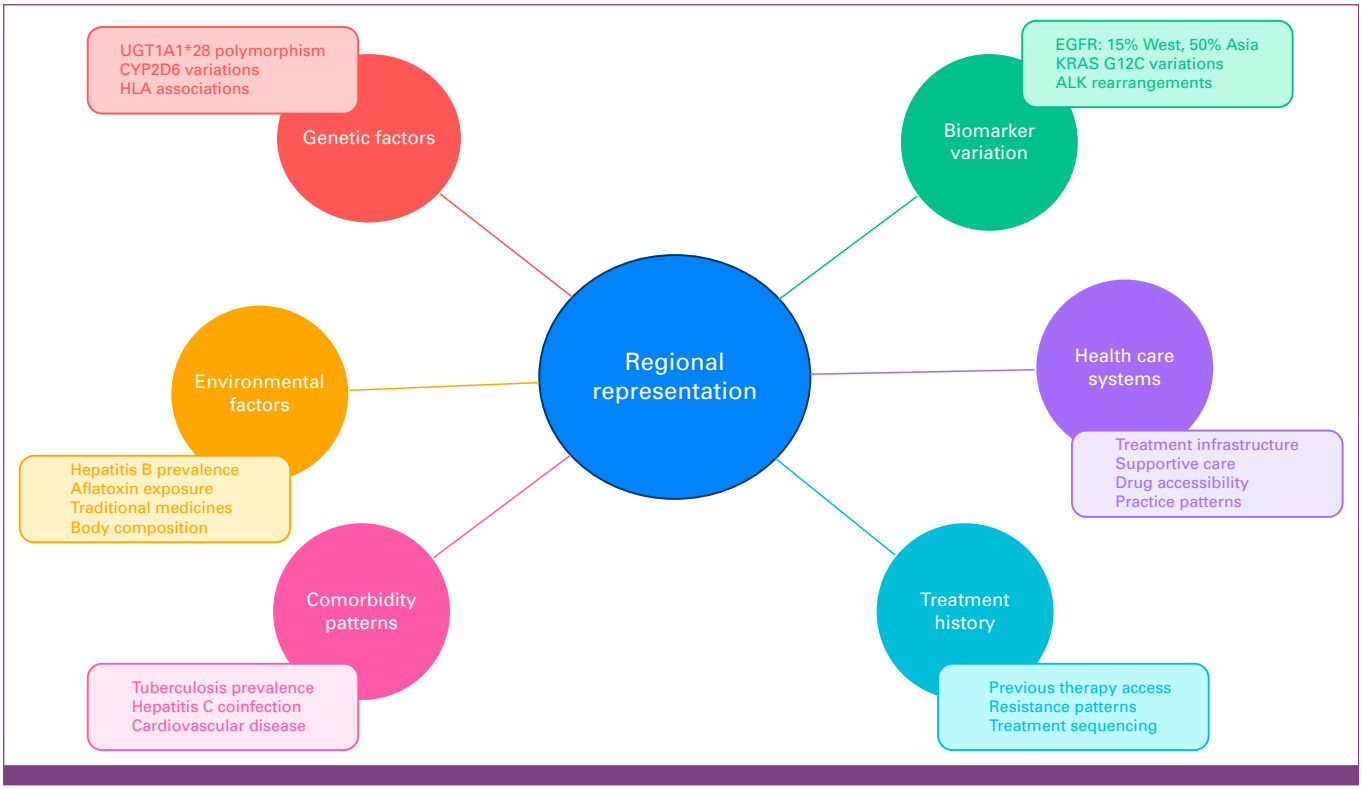


**FIG 1.** Scientific rationale for regional representation. HLA, human leukocyte antigen.

### Practical Implementation Considerations

Regional stratification strategies must consider the trade-off between granularity and statistical power. Over-stratification can lead to small regional sample sizes that preclude meaningful analysis, while understratification may mask important regional differences.

A pragmatic approach involves defining super-regions on the basis of regulatory, clinical practice, and biological similarity. For example: North America, Europe, Asia-Pacific, and Rest of the World groupings often provide sufficient granularity while maintaining adequate sample sizes.[18]

## SAMPLE SIZE IMPLICATIONS AND POWER CONSIDERATIONS

### Impact on Overall Trial Size

Regional enrollment requirements do not necessarily mandate larger overall trial sizes, but they do impose constraints on enrollment distribution that can affect study duration and feasibility. The key consideration is whether regional subgroup analyses require independent powering or can rely on consistency assessments.

For most registrational trials, the primary analysis remains the overall population comparison, with regional analyses serving as supportive evidence. This approach maintains overall sample size efficiency while providing regional insights.

However, when regulatory agencies require demonstration of efficacy within specific regions (as sometimes occurs in Asia-Pacific submissions), additional sample size considerations become necessary. In such cases, the trial may need to be powered for the smallest regional subgroup of interest.

### Adaptive Approaches to Regional Enrollment

Adaptive trial designs offer innovative solutions to regional enrollment challenges. Group sequential designs can incorporate regional enrollment milestones, allowing for trial modification if regional recruitment patterns deviate from expectations.

Adaptive randomization schemes can dynamically adjust allocation ratios to optimize regional balance without compromising overall trial efficiency. These approaches are particularly valuable in rare cancer indications where regional enrollment patterns are unpredictable (Fig 2 and Table 2).[19]

## FUTURE DIRECTIONS AND RECOMMENDATIONS

### Regulatory Harmonization

The oncology community should advocate for greater regulatory harmonization around regional enrollment

**TABLE 1.** Comprehensive Data Transportability Assessment in Cancer Clinical Trials

| Clinical Data Category | Transportability Level | Key Considerations | Regional Validation Requirements | Examples |
|---|---|---|---|---|
| Primary efficacy end points | High | OS and PFS generally translate well when treatment effects are robust and biologically plausible | Minimal—consistency assessment sufficient | Median OS, PFS hazard ratios across populations |
| Mechanistic end points | High | Biomarker responses and pharmacodynamic measures remain consistent when biological pathways are conserved | Low—pathway validation recommended | Target engagement biomarkers, pharmacodynamic responses |
| Safety profiles | Moderate-high | Adverse event patterns broadly similar; frequency and severity may vary | Moderate—population-specific monitoring | Dose-limiting toxicities, grade 3-4 AE rates |
| Predictive biomarkers | High | Valid across populations when backed by strong biological rationale | Low-moderate—analytical validation | Companion diagnostics, mutation-specific responses |
| Dose optimization | Variable | May require regional adjustment for differences in body composition, genetic factors, or tolerance patterns | High for certain populations | BSA-based dosing, ethnic-specific pharmacokinetics |
| Drug-drug interactions | Variable | Differs by medication usage patterns, genetic polymorphisms, and traditional medicine practices | High—population-specific studies needed | CYP450 interactions, traditional medicine combinations |
| Quality-of-life outcomes | Low | Influenced by cultural differences in symptom perception, health care expectations, and QoL priorities | High—cultural adaptation essential | Patient-reported outcomes, symptom scales |
| Health care resource utilization | Low | Highly region-specific because of health care delivery models, reimbursement systems, and practice patterns | High—local economic validation required | Hospital stay duration, outpatient visits, cost analyses |

Abbreviations: AE, adverse events; OS, overall survival; PFS, progression-free survival; QoL, quality of life.



expectations. Consistent international standards would reduce duplicative requirements and enable more efficient global trial designs.

Collaboration between regulatory agencies through initiatives such as the ICH process can establish evidence standards that balance global efficiency with regional relevance. Real-world evidence integration offers additional opportunities to supplement traditional trial data with region-specific insights.

### Technological and Analytical Innovations

Emerging technologies can address regional enrollment challenges more effectively:

Machine learning approaches can identify optimal regional enrollment strategies on the basis of historical trial data and population characteristics.

Real-world evidence platforms can provide complementary regional data to support traditional trial evidence, potentially reducing regional enrollment requirements.

Digital health technologies can enable more efficient regional outcome collection and analysis, supporting quality of life and health care utilization end points.[20]

The recent IQVIA report (ref) notes evolution in the European Union (EU) framework through decentralized clinical trials integration (43% of oncology trials now use hybrid designs combining site visits with telemedicine) and artificial intelligence-enhanced forecasting (a pilot program is using historical data from the EU's clinical trials information system to predict optimal site locations—with 87% accuracy in a 2023 test, enrollment timelines—with ±9 days variance, and real-world data linkages offering automatic connections to cancer registries in 11 member states).

## PRACTICAL IMPLEMENTATION FRAMEWORK

Organizations conducting global cancer trials should develop systematic approaches to regional considerations:

1. Early stakeholder engagement with regional regulatory agencies and clinical communities to understand local expectations and constraints
2. Integrated regional planning that considers enrollment feasibility, regulatory requirements, and scientific objectives
3. Adaptive design capabilities that can respond to evolving regional enrollment patterns
4. Standardized regional analysis frameworks that provide consistent approaches across development programs

The IQVIA report recommends that sponsors should look to integrate both readiness-tier countries (eg, Poland, Belgium, and Denmark) and opportunity-tier countries (eg, India, Brazil, and South Africa) into phase II/III oncology programs. Its findings support the broader calls for harmonized regulatory standards (eg, ICH E17), regional incentives for including local populations, and the investments that will be necessary in infrastructure and training in many less-developed countries that might be chosen for inclusion in trial programs.

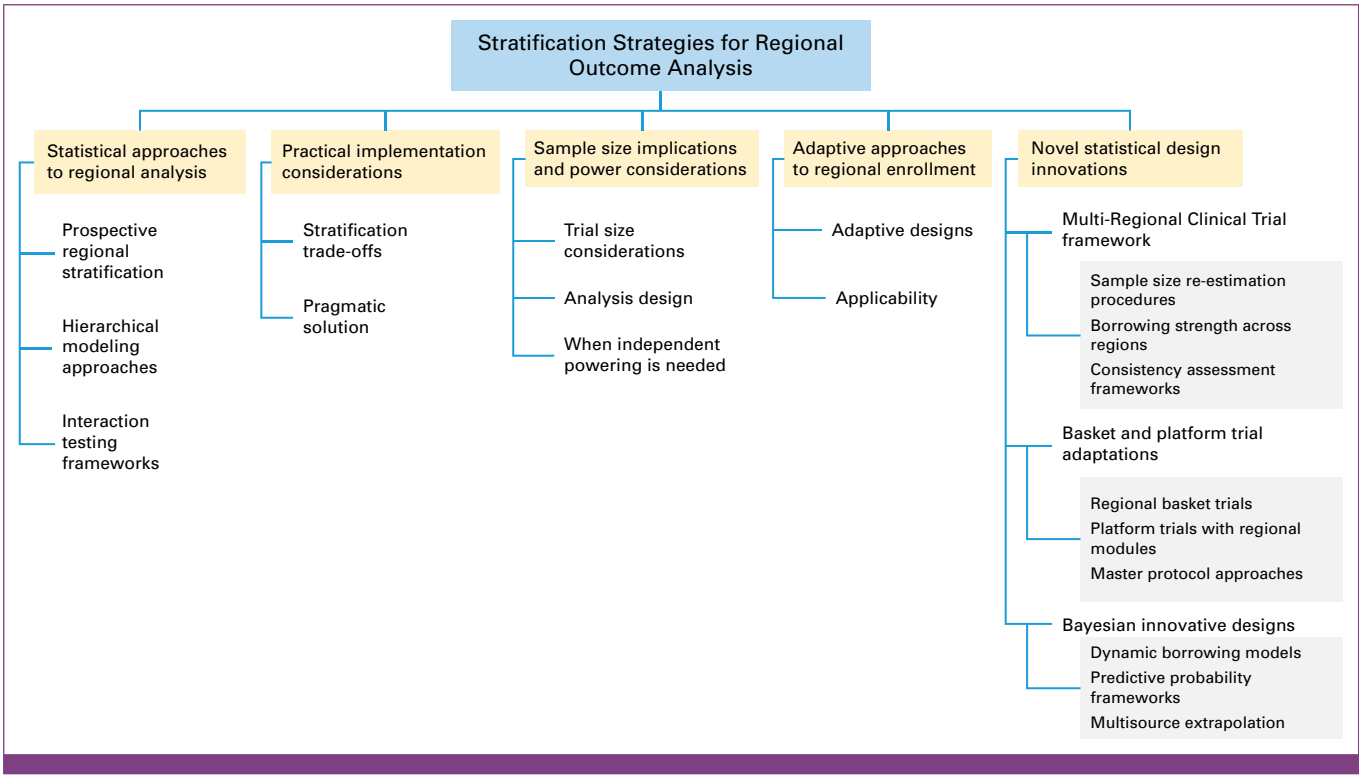


**FIG 2.** Stratification strategies for regional outcome analysis.

It also cites the WHO Essential Medicines List Committee's encouragement in 2024 for timely trial registration, which characterized this as not just an administrative hurdle but as the bedrock of regional data validity, that, in an era of decentralized trials, sponsors must treat as non-negotiable scientific rigor. In addition to ensuring ethical recruitment in regional trials by preventing exploitation of vulnerable populations in high-enrolling regions, it can also protect data transportability by locking in regional stratification plans before enrollment biases emerge. This in turn can accelerate approvals by reducing delays from regulatory queries for compliant trials.

## Turning Challenge Into Opportunity

Contemporary conditions have presented the clinical trial community with a chance to improve better patient care by choices that can promote both global efficiency and regional relevance. The IQVIA report not only highlights current constraints but also prompts suggestions of how

**TABLE 2.** ICH E17 MRCT Framework Components

| MRCT Component | Description | Implementation Approach | Benefits | Considerations |
|---|---|---|---|---|
| Sample size re-estimation | Dynamic adjustment of regional targets on the basis of observed enrollment patterns and interim effect estimates | Adaptive protocols with preplanned interim analyses | Maintains regional representation and overall trial power | Requires robust statistical planning and regulatory alignment |
| Bayesian borrowing across regions | Leverages data across regions to provide region-specific estimates even with modest individual regional sample sizes | Hierarchical Bayesian models with dynamic borrowing | Enables regional insights with smaller sample sizes | Complex methodology requiring specialized expertise |
| Consistency assessment framework | Formal evaluation of treatment effect consistency across regions using predefined criteria | Prespecified statistical tests and confidence interval approaches | Supports regulatory decision making with objective criteria | Must balance sensitivity with practical implementation |
| Regional stratification | Balanced treatment allocation within major geographic regions | Stratified block randomization or minimization | Ensures interpretable regional subgroup analyses | May increase complexity and sample size requirements |
| Adaptive regional enrollment | Real-time adjustment of regional recruitment on the basis of enrollment patterns | Group sequential designs with regional milestones | Optimizes enrollment efficiency and regional balance | Requires sophisticated trial management systems |

Abbreviations: ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; MRCT, Multi-Regional Clinical Trial.

stakeholders can positively advance scientific validity of trials while assuring their greater resilience in the face of growing geopolitical instability.

It depicts an international biopharma clinical research ecosystem reshaped by 5 years of technological, environmental, societal, regulatory, and geopolitical shifts that fueled execution challenges, delays, capacity concerns, and uncertainty, resulting in slower clinical development program timelines and negative impacts on patient treatment options and outcomes. Clinical trial enrollment durations have been increasing over the past 5 years across all phases and therapeutic areas, but particularly for oncology, and the average time from trial start to patient enrollment close for all trials in the pipeline increased by 26% from 2019 to 2023. Against this background, it argues that clinical trial country prioritization has become a critical focus. It warns of recruitment challenges in saturated geographies or therapeutic areas, aggravated by geopolitical volatility, viral outbreaks, and transition to a multipolar world. To overcome global, regional, and local trial enrollment and execution disruptions and to alleviate bottlenecks and enable agility, it urges clinical trial global diversification, highlighting opportunities for multistakeholder investment to extend clinical research global options through expanding the pool of countries suitable for clinical trials.

Meanwhile, concentration of trial activity by country is high, with the 10 leading countries being responsible for 58% of the total clinical trial country-uses from 2021 to 2023, and a disproportion in disease incidence and trial participation. It points out that in oncology, India accounts for 6% of the global cases, but only 2% of clinical trials—exemplifying a trend where countries with high patient availability exhibit operational gaps that prevent them from being used in clinical trials in proportion to the patient need.[21]

## REGULATORY AGENCY PERSPECTIVES ON REGIONAL ENROLLMENT

### US FDA Approach to US Enrollment

The FDA has evolved its perspective on regional enrollment over the past decade, moving from relatively flexible approaches to more structured expectations. The FDA's current position, articulated through various guidance documents and regulatory communications, emphasizes that although global trials are acceptable, adequate US representation is crucial for understanding how therapies will perform in the US health care environment.

### Quantitative Expectations

Although the FDA does not mandate specific percentages, informal guidance suggests that US enrollment of 20%-40% in global registrational trials provides sufficient representation for most oncology indications. However, this expectation varies significantly on the basis of the mechanism of action, patient population, and available alternative therapies.

### Bridging Study Requirements

When US enrollment falls below acceptable thresholds, the FDA may require additional bridging studies or US-specific safety run-ins. For novel mechanisms of action or first-in-class agents, the agency often shows greater flexibility, recognizing the global nature of drug development for breakthrough therapies.

### Standard-of-Care Considerations

The FDA places particular emphasis on ensuring that control arms reflect US standard-of-care practices. This requirement has become more stringent as treatment landscapes evolve rapidly, particularly in immune-oncology combinations where US practice patterns may differ significantly from other regions.

### Postmarket Commitments

The FDA increasingly uses postmarket study requirements to address regional enrollment concerns, allowing for accelerated approval pathways while ensuring that US-specific questions are addressed through confirmatory studies or expanded access programs.[22]

## EMA REGIONAL PERSPECTIVES

The EMA's approach to European enrollment reflects the complexity of the European Union's diverse health care systems and regulatory framework. Unlike the FDA's single-market focus, the EMA must consider variation across 27 member states with different health care infrastructures, clinical practices, and patient populations.

### Flexible Regional Requirements

The EMA generally adopts a more flexible approach to European enrollment percentages, focusing on the scientific rationale for regional representation rather than rigid numerical targets. The agency emphasizes that European enrollment should be sufficient to characterize safety and efficacy in the intended European patient population.

### Central Versus National Perspectives

Although the EMA provides centralized scientific assessment, individual member states may have additional requirements for national reimbursement decisions. Countries such as Germany and France often expect substantial local enrollment to support health technology assessments, creating additional complexity for sponsors.

### Reference Member State Considerations

The EMA's decentralized procedure allows for reference member state designation, which can influence enrollment strategies. Sponsors often prioritize enrollment in countries likely to serve as reference states for subsequent approvals.

### Pediatric and Rare Disease Flexibility

The EMA shows particular flexibility for pediatric oncology and rare cancer indications, recognizing that European enrollment targets may be unrealistic, given small patient populations and specialized treatment centers.[23]

## ASIA-PACIFIC REGULATORY LANDSCAPE

### Japan PMDA Requirements

The Pharmaceuticals and Medical Devices Agency in Japan has historically required the most stringent regional enrollment standards, often expecting 50% or higher Japanese enrollment in global trials, or separate Japanese bridging studies. However, recent regulatory reforms have introduced more flexibility, particularly for oncology indications with high unmet medical need.

The PMDA's evolving approach includes acceptance of Asian enrollment data for bridging purposes and recognition of global trial data when treatment effects are consistent and biologically plausible. The agency has also implemented consultation frameworks that allow for early discussion of regional enrollment strategies.

### Other Asian Regulatory Authorities

Countries including South Korea, Taiwan, and Singapore have developed increasingly sophisticated approaches to regional enrollment. These agencies often accept Asia-Pacific regional data as adequate representation, recognizing shared genetic and environmental factors across East Asian populations.

### China NMPA Considerations

The National Medical Products Administration in China has undergone significant regulatory reform, moving from requirements for entirely separate Chinese studies toward acceptance of global trial data with adequate Chinese enrollment. Current expectations suggest 20%-30% Chinese enrollment in global registrational trials, although this varies by indication and mechanism of action.[24]

## OTHER REGIONAL REGULATORY CONSIDERATIONS

### Health Canada Approach

Canada's regulatory approach generally aligns with FDA expectations, with informal guidelines suggesting 10%-20% Canadian enrollment for most oncology indications. Health Canada often accepts US-heavy North American enrollment as adequate representation, given similarities in health care systems and clinical practices.

### Australian Therapeutic Goods Administration Perspectives

The Therapeutic Goods Administration typically accepts global trial data without specific Australian enrollment requirements, particularly for oncology indications. However, the Pharmaceutical Benefits Advisory Committee may consider local enrollment in reimbursement decisions.

### Latin American Regulatory Harmonization

Countries including Brazil, Mexico, and Argentina have developed increasingly coordinated approaches to regional enrollment through initiatives such as PANDRH. These agencies generally accept global trial data with modest regional representation, focusing on safety and efficacy consistency rather than specific enrollment percentages (Fig 3).

## STANDARD-OF-CARE CONTROL ARM CHALLENGES

One of the most complex aspects of regional enrollment strategy involves managing different standards of care across regions, which directly affects control arm selection and trial interpretation.

### Geographic Variation in Treatment Paradigms

Standard of care can vary dramatically across regions because of drug availability, reimbursement policies, clinical guideline differences, and health care infrastructure limitations. For example, immune checkpoint inhibitor access varies significantly between developed and emerging markets, affecting control arm selection for combination studies.

### Regulatory Acceptance of Global Controls

Regulatory agencies increasingly scrutinize whether control arms reflect local standard-of-care practices. The FDA may question trial results if US patients received control treatments that differ substantially from standard US practice, while the EMA must consider variation across European member states.[25]

### Innovative Control Arm Strategies

Sponsors have developed several approaches to address standard-of-care variation:

- Regional stratification with flexible controls: Allowing different control regimens across regions while maintaining randomization balance

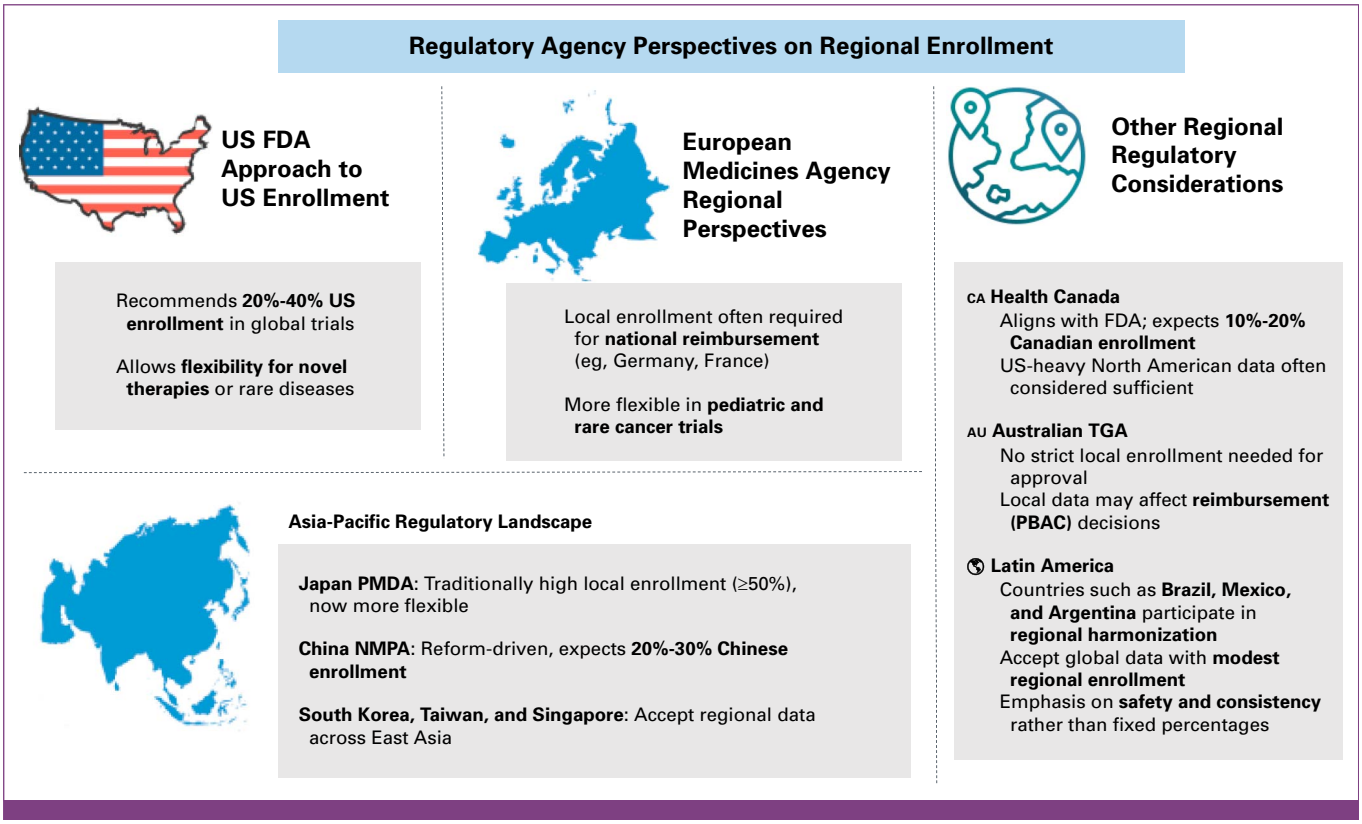


**FIG 3.** Regulatory agency perspectives on regional enrollment. FDA, US Food and Drug Administration; NMPA, National Medical Products Administration; PBAC, policy-based access control; PMDA, Pharmaceuticals and Medical Devices Agency; TGA, Therapeutic Goods Administration.

- Physician choice controls: Permitting investigators to select among several acceptable standard-of-care options on the basis of local practice
- Time-adjusted historical controls: Using region-specific historical data to supplement trial controls when standard of care evolves during study conduct

## Ethical Considerations

Different regional standards of care raise ethical questions about equipoise and patient care. Sponsors must ensure that control arms provide appropriate care across all participating regions while maintaining scientific validity.

## Postmarket Evidence Generation

Regulatory agencies increasingly expect postmarket studies to address standard-of-care questions that cannot be fully resolved in registrational trials. Real-world evidence generation can help bridge differences between trial controls and actual clinical practice across regions.

## Impact on Regulatory Decision Making

Standard-of-care variations can significantly influence regulatory decisions. The FDA may discount efficacy results if control arms do not reflect US practice, while emerging market regulators may question the relevance of trials using expensive control regimens not available locally.

## Future Harmonization Efforts

International initiatives such as ICH E17 implementation aim to develop frameworks for managing standard-of-care variation in global trials. These efforts focus on pretrial regulatory alignment and adaptive trial designs that can accommodate regional practice differences.[26]

In conclusion, regional enrollment considerations in cancer registrational trials represent both a challenge and an opportunity for the oncology community. Although they add complexity to trial design and analysis, they also enhance the global relevance and applicability of clinical research. In addition, unstable global conditions underscore the need for a broader, more resilient global footprint, which judicious regional enrollment can help secure. Success requires moving beyond viewing regional enrollment as a regulatory burden toward embracing it as a scientific opportunity to generate more robust and applicable evidence. Through innovative statistical designs, adaptive methodologies, and collaborative regulatory engagement, the field can develop approaches that satisfy both global efficiency and regional relevance. The future of cancer drug development depends on our ability to conduct trials that generate compelling

evidence for diverse global populations while maintaining scientific rigor and regulatory acceptability. Regional enrollment strategies, when thoughtfully implemented, can enhance rather than compromise this objective. As we advance toward more personalized and precise cancer care, regional considerations will likely become even more important. Proactive development of frameworks, methods, and collaborative approaches will position the oncology community to meet these evolving challenges while continuing to deliver life-saving therapies to patients worldwide, because, as President John F. Kennedy once observed, "*A rising tide lifts all boats*." When we elevate the quality and inclusivity of regional enrollment practices in cancer trials, we lift the entire enterprise of global drug development, ensuring that innovative therapies reach and benefit patients across all continents and populations.

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