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Consensus Methods in Regulatory Affairs: A Decision Framework for Cell and Gene Therapies

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Abstract

Regulatory decision-making frequently requires expert judgment when empirical evidence is limited, evolving, conflicting, or ethically complex. This challenge has become increasingly pronounced with the development of cell and gene therapies (CGTs), including products regulated as advanced therapy medicinal products (ATMPs) within the European Union, where product complexity, individualized manufacturing, limited patient populations, uncertain durability of therapeutic effect, and long-term safety considerations often extend beyond the scope of conventional regulatory evaluation. Although consensus methods are widely used to support regulatory deliberation, practical guidance on selecting the most appropriate methodology for a specific regulatory question remains limited.

This article proposes a decision framework for the systematic selection and application of consensus methods in regulatory affairs. The framework distinguishes between implicit consensus, which supports timely expert interpretation under conditions of scientific uncertainty, and explicit consensus, which provides structured, transparent, reproducible, and auditable approaches for decisions requiring regulatory consistency and broader harmonization. It further demonstrates how individual consensus methodologies may be combined through hybrid approaches and introduces a structured process for aligning consensus method selection with the expertise required to address the regulatory question.

Rather than viewing consensus solely as a mechanism for achieving agreement, this framework positions consensus as a regulatory governance strategy that aligns methodological rigor with evidentiary uncertainty, decision context, and regulatory objectives. By providing a systematic approach to consensus method selection, the proposed framework supports more transparent, reproducible, and internationally applicable regulatory decision-making throughout the development and lifecycle management of CGTs.

Keywords: Cell and Gene Therapies, Consensus Methods, Implicit Consensus Methods, Explicit Consensus Methods, Fast-Track Delphi, Regulatory Decision-Making, Global Regulatory Harmonization

Section 1. Introduction

Cell and gene therapies (CGTs) have transformed the therapeutic landscape by offering the potential to treat, modify, or cure diseases that were previously considered untreatable. Unlike conventional medicinal products, CGTs frequently involve complex biological mechanisms, individualized or platform-based manufacturing, limited clinical populations, evolving manufacturing processes, uncertain treatment durability, and long-term safety considerations. These characteristics challenge traditional regulatory paradigms because critical regulatory decisions often must be made before all scientific uncertainties have been fully resolved. Consequently, regulators must balance timely patient access with the responsibility to ensure product quality, safety, efficacy, and a favorable benefit-risk profile throughout the product lifecycle.[1,2,3,4,5,6,7]

As the complexity of CGTs has increased, regulatory decision-making has expanded beyond the evaluation of empirical evidence alone. Regulators must integrate multidisciplinary scientific expertise, clinical judgment, manufacturing knowledge, statistical evaluation, and patient considerations when evidence is incomplete, conflicting, or rapidly evolving. Under these circumstances, consensus functions as more than a mechanism for achieving expert agreement. Within regulatory science, it provides a governance process that integrates diverse scientific perspectives, reduces interpretive uncertainty, and supports transparent, reproducible, and scientifically defensible regulatory decisions while maintaining public health accountability.[8,9,10]

The need for structured consensus is reinforced by the global development of CGTs. Although major regulatory authorities including the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), the Medicines and Healthcare products Regulatory Agency (MHRA), Health Canada (HC), and China's National Medical Products Administration (NMPA) share the common objective of protecting public health, they operate within different legal and regulatory frameworks, resulting in differences in evidentiary expectations, regulatory pathways, and long-term oversight. International organizations, including the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), the World Health Organization (WHO), and the Organisation for Economic Co-operation and Development (OECD), further promote convergence through harmonized technical guidance, scientific standards, and policy recommendations. Within this complex regulatory environment, structured consensus methodologies provide a transparent and reproducible mechanism for supporting consistent scientific interpretation and international regulatory harmonization.[11]

Consensus methodologies are well established across medicine, public health, healthcare research, guideline development, health technology assessment, and regulatory science. However, the increasing complexity of CGTs highlights the need for a systematic approach to selecting the consensus methodology most appropriate for a given regulatory question. Different methodologies are designed to address different objectives, evidentiary contexts, stakeholder interactions, governance requirements, and intended regulatory outputs. Accordingly, this article reviews the principal implicit, explicit, and hybrid consensus methodologies applicable to regulatory science and proposes a structured decision framework for selecting the most appropriate methodology according to the regulatory question. The framework further introduces a systematic process for aligning subject-matter expert (SME) selection with the selected consensus methodology, recognizing that participant selection should follow methodological design rather than precede it. By integrating established consensus methodologies within a practical regulatory decision architecture, the proposed framework supports more transparent, reproducible, and internationally harmonized regulatory decision-making throughout the lifecycle of CGTs. [8,9,10]

Section 2. Consensus in Regulatory Science

Consensus is a structured process for integrating the knowledge, experience, and judgment of multiple experts to support decision-making when empirical evidence alone is insufficient to resolve a scientific or regulatory question. Although the concept is widely used across medicine, public health, healthcare research, and policy development, consensus is not simply synonymous with agreement. Rather, it is a systematic approach to evaluating evidence, resolving differences in interpretation, and producing decisions that are transparent, justifiable, and appropriate for their intended purpose.[8,9,10,12]

Within regulatory science, consensus serves an important governance function by enabling multidisciplinary experts to evaluate complex scientific questions that extend beyond the scope of established regulatory standards. This is particularly relevant for innovative products such as CGTs, where rapidly evolving science, limited clinical experience, novel manufacturing technologies, and long-term uncertainties frequently require regulatory interpretation before comprehensive evidence is available. Under these circumstances, consensus provides a structured means of integrating scientific expertise while maintaining transparency, consistency, and regulatory accountability.[1,4,6,9]

Consensus methodologies differ considerably in their degree of structure, participant interaction, documentation, reproducibility, and intended regulatory application. Some approaches rely primarily on expert discussion and professional judgment, whereas others employ predefined procedures, structured feedback, quantitative scoring, or iterative rounds of evaluation. Consequently, consensus should not be viewed as a single methodology but rather as a family of complementary approaches that can be selected according to the characteristics of the regulatory question, the available evidence, the level of uncertainty, and the intended regulatory outcome.[9,10]

From a regulatory perspective, consensus methodologies can be broadly categorized into two complementary groups: implicit consensus and explicit consensus. Implicit consensus develops through expert deliberation, scientific interpretation, and professional experience without predefined procedural rules, whereas explicit consensus employs structured methodologies with documented procedures, predefined criteria, and reproducible processes. Neither approach is inherently superior. Instead, each serves different regulatory purposes and should be selected according to the nature of the scientific question, the governance requirements, and the desired regulatory output. [9,10]

Increasingly, regulatory decision-making also incorporates hybrid consensus models that combine elements of both implicit and explicit methodologies. Hybrid approaches recognize that complex regulatory questions often require the flexibility of expert interpretation together with the transparency and reproducibility provided by formal consensus methods. This is particularly relevant for CGTs, where decisions may encompass Chemistry, Manufacturing and Controls (CMC), non-clinical evaluation, clinical development, long-term safety, patient perspectives, and ethical considerations within a single regulatory assessment. [9,10]

Accordingly, the following sections examine the principal categories of consensus methodologies used in regulatory science. Section 3 reviews implicit consensus approaches and their role in the early interpretation of emerging evidence. Section 4 examines explicit consensus methodologies designed to support transparent and reproducible decision-making. These concepts provide the foundation for the regulatory decision framework presented later in the manuscript, which proposes a systematic approach for selecting the consensus methodology most appropriate for a given regulatory question. [9,10]

Section 3. Implicit Consensus Methods in Regulatory and Health Science

Not all regulatory questions require highly structured consensus methodologies. During the early evaluation of innovative products, regulators frequently encounter situations in which scientific evidence is limited, evolving, conflicting, or incomplete. This is particularly true for cell and gene therapies (CGTs), where novel biological mechanisms, individualized or platform-based manufacturing, limited clinical experience, and small patient populations often require regulatory interpretation before comprehensive evidence or regulatory precedents become available. Under these circumstances, implicit consensus provides a practical and scientifically appropriate mechanism for integrating expert judgment while supporting timely regulatory decision-making.[1,5,6]

Implicit consensus is characterized by the integration of multidisciplinary expertise through professional deliberation, scientific interpretation, precedent-based reasoning, and shared regulatory experience without predefined scoring systems, voting thresholds, or iterative consensus procedures. This flexibility makes implicit consensus particularly valuable when scientific uncertainty exceeds the available evidence, reflecting the practical reality that regulatory science often requires expert interpretation before sufficient evidence exists to justify more formalized consensus methodologies. Consequently, implicit consensus serves as an important component of regulatory governance by enabling scientifically defensible decisions while preserving the flexibility needed to respond to rapidly evolving technologies.[8,9,10]

Within CGT development and regulation, implicit consensus is particularly valuable during the assessment of novel products, emerging manufacturing platforms, innovative gene-editing technologies, first-in-human clinical studies, evolving potency assays, vector persistence, manufacturing comparability, and long-term safety considerations. In these situations, regulatory interpretation often depends on biological plausibility, accumulated scientific experience, analogical reasoning, institutional knowledge, and multidisciplinary discussion to bridge evidence gaps until additional clinical or manufacturing data become available. These interpretive processes allow development and regulatory evaluation to progress while maintaining scientific rigor despite residual uncertainty.[1,4,5,6,13]

Implicit consensus encompasses several complementary approaches that support different regulatory needs, ranging from informal multidisciplinary deliberation and experience-based decision-making to interpretive evidence integration, precedent-based case review, and leadership-guided synthesis. These approaches differ primarily in how expert knowledge is integrated and applied rather than in their shared objective of supporting scientifically defensible regulatory interpretation. Their principal characteristics, representative regulatory applications, strengths, and limitations are summarized in Table 1. Collectively, these methodologies provide the flexibility needed to support regulatory decision-making when scientific evidence is limited, rapidly evolving, or insufficient to justify more structured consensus approaches.[8,9,10]

The same flexibility that makes implicit consensus valuable also creates important governance challenges. Because the process does not rely on predefined procedures or standardized documentation, the scientific rationale underlying regulatory decisions may be difficult to reproduce, audit, or compare across reviewers and jurisdictions. Similar evidence may therefore be interpreted differently depending on institutional experience, available expertise, or regulatory context. These limitations do not diminish the scientific value of implicit consensus; rather, they emphasize the importance of documenting the reasoning process whenever its conclusions may influence future regulatory policy, guidance development, or harmonization activities.[9,10]

Accordingly, implicit consensus should be regarded as an early interpretive governance mechanism rather than a complete regulatory solution. It is particularly appropriate for exploratory, urgent, case-specific, or biologically novel regulatory questions where flexibility and scientific interpretation are essential. As evidence accumulates and regulatory expectations mature, however, conclusions initially derived through implicit consensus should be documented systematically and, where broader consistency, reproducibility, or international harmonization is required, transitioned to more structured explicit consensus methodologies. [9,10]

Table 1 summarizes the principal forms of implicit consensus encountered in regulatory and health science, together with their defining characteristics, representative regulatory applications, and principal limitations. Rather than ranking one methodology over another, the table illustrates that implicit consensus comprises a family of complementary interpretive approaches, each suited to different regulatory questions and evidentiary contexts. The critical consideration is not identifying the "best" method but selecting the approach that is proportionate to the scientific uncertainty, urgency, governance requirements, and intended regulatory application. [9,10]

Table 1. Implicit Consensus Methodologies and their Regulatory Applications.

Methodology	Primary Mechanism	Regulatory Applications	Strengths	Limitations
Informal Expert Deliberation	Unstructured multidisciplinary discussion	Early interpretation of novel CGT evidence	Flexible, rapid, multidisciplinary	Limited transparency and auditability
Naturalistic Decision-Making	Experience-based pattern recognition	Urgent assessments and emerging safety issues	Efficient, experience-driven	Susceptible to cognitive bias
Interpretive Consensus (Sensemaking)	Narrative integration of heterogeneous evidence	Integration of CMC, non-clinical, clinical, and RWD	Holistic interpretation	Variable reproducibility
Rapporteur/Case Review Synthesis	Precedent-based dossier interpretation	Scientific advice and dossier evaluation	Uses accumulated regulatory knowledge	Dependent on reviewer expertise

Methodology	Primary Mechanism	Regulatory Applications	Strengths	Limitations
Leadership-Driven Consensus	Senior expert synthesizes multidisciplinary input	Time-sensitive governance decisions	Efficient decision-making	Potential hierarchy bias

The methodologies summarized in Table 1 demonstrate that implicit consensus provides an essential foundation for regulatory decision-making when scientific evidence is limited or rapidly evolving. However, as regulatory decisions become more consequential, require broader stakeholder participation, or are intended to support regulatory guidance, policy development, or international harmonization, greater methodological structure becomes necessary. These circumstances call for explicit consensus methodologies, which provide the transparency, reproducibility, and auditability required for decisions that extend beyond individual cases and influence broader regulatory practice. [9,10]

Section 4. Explicit Consensus Methods in Regulatory and Health Science

Explicit consensus methods use predefined procedures to structure expert judgment through systematic participant selection, iterative feedback, scoring, ranking, voting, or predefined agreement thresholds. Unlike implicit consensus, where agreement emerges primarily through professional deliberation and shared interpretation, explicit methodologies employ transparent and reproducible processes that allow the consensus-building process itself to be documented, evaluated, and, when appropriate, replicated. As a result, explicit consensus methods are particularly valuable when regulatory decisions must extend beyond individual cases to inform guidance development, policy, harmonization initiatives, or other decisions requiring a clearly documented evidentiary foundation.

Within regulatory science, explicit consensus methods extend beyond research tools by providing structured mechanisms for transforming scientific uncertainty into recommendations, decision criteria, and governance frameworks that can be applied consistently across multidisciplinary teams and regulatory jurisdictions. Their importance is particularly evident in cell and gene therapies (CGTs), where limited clinical experience, rapidly evolving technologies, and heterogeneous evidence frequently require systematic expert evaluation before universally accepted regulatory standards can be established.[8,9,10]

Classical Delphi

The Classical Delphi method is the most widely recognized explicit consensus methodology. It is based on multiple rounds of anonymous questionnaires, structured feedback, and controlled iteration, allowing experts to reconsider their responses after reviewing aggregated panel results. This iterative process minimizes the influence of dominant personalities, encourages independent judgment, and gradually moves the group toward consensus. Within regulatory science, Classical Delphi is particularly useful for developing definitions, identifying critical evaluation criteria, prioritizing research needs, establishing regulatory expectations, and supporting guidance development when empirical evidence alone is insufficient.[14-20]

Fast-Track Delphi

Fast-Track Delphi applies the same underlying principles as the Classical Delphi method but is designed for situations requiring more rapid decision-making. By reducing the number of surveys rounds and using digital platforms, accelerated feedback cycles, or real-time synthesis, it shortens the consensus process while preserving methodological structure. This approach is especially valuable when regulatory agencies must respond to emerging safety concerns, rapidly evolving technologies, or public health emergencies. The principal trade-off is that greater efficiency may reduce deliberative depth, making careful documentation of participant selection, response rates, consensus thresholds, and analytical methods particularly important.[21-23]

Nominal Group Technique

The Nominal Group Technique (NGT) combines structured individual idea generation with facilitated group discussion and prioritization. Unlike Delphi methodologies, which emphasize anonymity and asynchronous participation, NGT relies on direct interaction while ensuring that each participant contributes independently before discussion begins. This structure promotes balanced participation, reduces the influence of dominant individuals, and enables efficient prioritization of complex issues. Within regulatory science, NGT is well suited for defining regulatory problems, identifying evaluation criteria, prioritizing risk domains, incorporating stakeholder perspectives, and generating candidate statements for subsequent Delphi or other structured consensus exercises.[24-27]

Consensus Development Conferences

Consensus Development Conferences (CDC) are deliberative consensus processes designed for questions that extend beyond scientific evidence to include ethical, societal, and public policy considerations. These conferences typically combine systematic evidence review, expert presentations, multidisciplinary panel discussions, and the development of formal consensus statements. Their principal strengths are transparency, broad stakeholder engagement, and public legitimacy. However, they are resource-intensive and may be less suitable when rapid consensus is required. Within the CGT field, CDC methodologies are particularly applicable to issues such as genome editing, equitable patient access, and other regulatory questions with significant societal implications. [29-32]

RAND/UCLA Appropriateness Method

The RAND/UCLA Appropriateness Method (RAM) integrates systematic evidence review with structured expert scoring to determine whether specific interventions or regulatory approaches are appropriate under defined circumstances. Unlike Delphi methodologies, which seek convergence of opinion, RAM produces quantitative appropriateness ratings that combine empirical evidence with expert judgment. Within regulatory science, RAM may support structured benefit-risk evaluations, assessment of long-term follow-up strategies, evaluation of manufacturing changes, and regulatory decisions where randomized clinical evidence is limited. Its structured scoring provides transparency but should be interpreted alongside qualitative discussion to avoid oversimplifying complex scientific or ethical considerations.[33-35]

Policy Delphi

Policy Delphi differs fundamentally from the Classical Delphi method because its primary objective is not consensus. Instead, it seeks to identify, characterize, and understand differing viewpoints by documenting areas of agreement, disagreement, and the reasoning underlying competing policy positions. This methodology is particularly valuable when regulatory questions involve ethical uncertainty, societal values, public acceptance, or competing stakeholder priorities. Rather than forcing convergence, Policy Delphi provides decision-makers with a structured understanding of the range of informed opinions that may influence future regulatory policy.[36-38]

Hybrid Consensus Models

Increasingly, complex regulatory questions are addressed through hybrid consensus models that combine complementary methodologies either sequentially or in parallel. For example, NGT may be used to generate candidate criteria, followed by Classical Delphi or Fast-Track Delphi to refine and prioritize them, RAM to evaluate appropriateness, and Policy Delphi to explore ethical or policy implications. Such combinations recognize that complex regulatory questions rarely involve a single dimension of scientific uncertainty. In CGTs, a single regulatory decision may simultaneously require evaluation of Chemistry, Manufacturing and Controls (CMC), non-clinical findings, clinical evidence, long-term safety, patient perspectives, and international regulatory expectations. Hybrid consensus models therefore provide the flexibility needed to balance methodological rigor with the complexity of real-world regulatory decision-making. [9,10]

Table 2 summarizes the principal explicit consensus methodologies discussed in this section, highlighting their defining strengths, principal limitations, and the regulatory contexts in which each method is most appropriately applied. Rather than identifying a universally preferred methodology, the table demonstrates that each explicit consensus approach has a distinct role within regulatory science and should be selected according to the characteristics of the regulatory question, the available evidence, stakeholder requirements, and the intended regulatory output.

Table 2. Explicit Consensus Methodologies and their Regulatory Applications.

Methodology	Primary Mechanism	Regulatory Applications	Strengths	Limitations
Classical Delphi	Anonymous iterative surveys with controlled feedback	Guidance development, endpoint definition, consensus criteria	Highly reproducible, minimizes dominance bias	Time-intensive
Fast-Track Delphi	Accelerated Delphi with digital feedback	Emerging safety issues, rapid policy development	Efficient and scalable	Less deliberative depth
Nominal Group Technique	Structured discussion with prioritization	Problem definition, stakeholder prioritization	Balanced participation	Limited scalability
Consensus Development Conference	Public multidisciplinary deliberation	Ethical, societal, and policy questions	Transparent, broad stakeholder engagement	Resource-intensive
RAND/UCLA Appropriateness Method	Evidence review combined with structured scoring	Benefit-risk evaluation, manufacturing changes, long-term follow-up	Quantitative and transparent	May oversimplify complex issues
Policy Delphi	Structured exploration of differing viewpoints	Ethical, access, and policy debates	Captures diverse perspectives	May not achieve consensus
Hybrid Models	Sequential or integrated combination of methods	Complex multidisciplinary CGT regulatory questions	Flexible and comprehensive	More complex to design and implement

The methodologies presented in Table 2 illustrate that explicit consensus is not a single process, but a family of structured approaches designed to address different forms of regulatory uncertainty. Some methods emphasize convergence, others prioritize stakeholder participation or appropriateness, while still others deliberately preserve differing viewpoints to inform policy development. Consequently, methodology selection should be driven by the regulatory question rather than familiarity with a particular technique. This understanding provides the foundation for the next section, which compares implicit and explicit consensus methodologies and examines how they complement one another across the regulatory lifecycle. [9,10]

Section 5. Comparison of Implicit and Explicit Consensus Methodologies

Having examined implicit and explicit consensus methodologies separately, it is now possible to compare their respective roles within regulatory science. Although both approaches seek to support scientifically sound regulatory decision-making, they are designed to address different types of regulatory questions, evidentiary

contexts, and governance requirements. Rather than representing competing methodologies, implicit and explicit consensus should be viewed as complementary approaches that can be applied independently, sequentially, or in combination according to the characteristics of the regulatory problem. [8,9,10]

The principal distinction between the two approaches lies in the degree of methodological structure required to support the intended regulatory outcome. Implicit consensus relies primarily on multidisciplinary expertise, professional judgment, scientific interpretation, and accumulated regulatory experience. It is particularly valuable when evidence is limited, rapidly evolving, or biologically novel, allowing regulators to reach timely and scientifically defensible conclusions despite residual uncertainty. Explicit consensus, by contrast, employs predefined methodologies that promote transparency, reproducibility, documentation, and consistency. These characteristics make explicit consensus particularly appropriate when regulatory decisions are expected to support guidance development, policy formation, cross-jurisdictional harmonization, or other activities requiring a clearly documented decision-making process.[1,4,6,9,10]

The distinction is especially relevant throughout the lifecycle of cell and gene therapies (CGTs). Early product development often requires interpretive judgments regarding novel manufacturing platforms, emerging analytical technologies, first-in-human clinical studies, or limited clinical datasets. Under these circumstances, implicit consensus provides the flexibility needed to integrate diverse scientific perspectives while allowing development to progress responsibly. As scientific knowledge accumulates and regulatory expectations become more clearly established, however, many of these same questions evolve into candidates for explicit consensus methodologies capable of producing standardized recommendations, consensus statements, appropriateness assessments, or harmonized regulatory expectations. In practice, regulatory decision-making frequently progresses from implicit interpretation toward explicit formalization as evidence matures and governance requirements increase.[26]

Table 3 compares the principal characteristics of implicit and explicit consensus methodologies across dimensions that are particularly relevant to regulatory science, including decision context, knowledge base, expected outputs, governance considerations, and their application throughout the CGT lifecycle. Rather than suggesting that one approach is inherently superior, the comparison demonstrates that each methodology provides distinct advantages under different regulatory circumstances. Consequently, the critical regulatory decision is not whether implicit or explicit consensus should be used universally, but which approach is most appropriate for the scientific question, the maturity of the available evidence, and the intended regulatory application.

Table 3. Comparison of Implicit and Explicit Consensus Methodologies

Dimension	Implicit consensus	Explicit consensus	Regulatory implication
Decision context	Novel, urgent, sparse evidence	Need for standardization or documentation	Use implicit early, explicit when outputs must travel across settings
Knowledge basis	Tacit expertise, precedent, pattern recognition	Structured elicitation, scoring, thresholds	Explicit methods improve auditability and external validity
Output	Narrative interpretation or position	Documented agreement, ranking, score, recommendation	Explicit outputs support harmonization matrices and guidance
Risk profile	Opacity, hierarchy, reviewer variability	Process rigidity, resource needs, artificial convergence	Hybrid designs can balance flexibility and rigor
CGT relevance	First-in-human, platform novelty, early safety interpretation	Endpoint consensus, long-term follow-up, benefit-risk, policy	Both are needed across the CGT lifecycle

Table 3 illustrates that implicit and explicit consensus methodologies occupy complementary positions within the regulatory decision-making continuum. Implicit consensus emphasizes interpretive flexibility and timely scientific judgment when uncertainty remains high, whereas explicit consensus emphasizes transparency, reproducibility, and standardized governance when decisions are intended to influence broader regulatory practice. Many regulatory questions will benefit from a progression between these approaches as evidence accumulates, while others may require hybrid strategies that combine elements of both methodologies.[9,10]

This comparison also introduces the principle of methodological proportionality, whereby the degree of methodological structure should be proportional to the characteristics of the regulatory question. Decisions involving exploratory science, urgent assessments, or emerging technologies may be appropriately addressed through implicit consensus, whereas decisions intended to establish regulatory guidance, harmonized standards, or enduring policy require more structured explicit methodologies. Selecting the appropriate consensus methodology is therefore a regulatory design decision rather than a procedural preference.[9,10]

Accordingly, the next section builds upon these comparative principles by introducing a structured decision framework that assists regulators in selecting the consensus methodology most appropriate for a given regulatory question before determining participant composition or subject-matter expertise. This framework translates the conceptual distinctions presented in the preceding sections into practical decision architecture for regulatory application.

Section 6. Framework for Consensus Method Selection

6.1 Framework Overview

The preceding sections established that implicit and explicit consensus methodologies address different regulatory questions, evidentiary contexts, and governance requirements. They also demonstrated that consensus methodologies are complementary rather than interchangeable, and that methodology selection should be driven by the regulatory question rather than familiarity with a particular technique. Building upon these principles, we propose a structured framework for consensus method selection that translates these concepts into a practical decision architecture for regulatory science.[9,10]

The framework is designed to assist regulatory scientists, multidisciplinary working groups, and policy developers in selecting the consensus methodology most appropriate for a specific regulatory question before identifying subject-matter experts (SMEs) or initiating the consensus process. This sequencing reflects a central principle of the proposed framework: consensus methodology selection should precede participant selection. Because the expertise required depends on the selected methodology and regulatory objective, identifying SMEs before selecting the consensus methodology may introduce bias into the design and implementation of the consensus exercise. [9,10]

The framework consists of four sequential decision trees that collectively guide the design of a regulatory consensus exercise. Figure 1 determines whether the regulatory question is best addressed through implicit or explicit consensus. Once that decision has been made, Figures 2 and 3 guide the selection of the most appropriate methodology within the chosen consensus family. Only after the methodology has been selected does Figure 4 address the identification and selection of appropriate SMEs. This sequence transforms consensus design into a structured, transparent, and reproducible process that aligns methodological rigor with the characteristics of the regulatory question.

The framework addresses three common challenges in regulatory consensus design: the assumption that Delphi is the default methodology regardless of the regulatory objective; the tendency to underestimate the methodological importance of implicit consensus in situations involving novel technologies or limited evidence; and the practice of assembling expert panels before selecting the most appropriate consensus methodology. By reversing this sequence, the framework aligns methodology selection with the regulatory question and participant selection with the chosen methodology. [9,10]

Accordingly, the framework should be viewed as a structured decision architecture rather than a prescriptive algorithm. Regulatory decision-making inevitably requires professional judgment, and consensus methodologies cannot replace scientific expertise or regulatory experience. Instead, the framework provides a transparent and reproducible process for selecting consensus methodologies that are proportionate to the regulatory question and sufficiently flexible to accommodate the diversity of challenges encountered throughout the regulation of medicinal products, including complex and rapidly evolving technologies such as cell and gene therapies.

6.2 Framework Implementation

The proposed framework is implemented through four sequential decision trees that guide the design of a consensus exercise from initial problem definition through participant selection. Each decision tree addresses a distinct methodological question while building upon the preceding step. Together, they provide a structured pathway for selecting a consensus methodology that is proportionate to the regulatory problem, the available evidence, and the intended regulatory outcome. Rather than functioning as independent algorithms, the four decision trees represent successive stages within a single consensus architecture.

The sequential organization reflects the dependent nature of regulatory consensus design. The initial decision is whether the regulatory question requires exploratory interpretation or formalized consensus. Once that distinction has been made, the appropriate methodology can be selected, followed by identification of the expertise needed to implement it. This progression minimizes methodological bias, improves transparency, and aligns participant selection with the objectives of the consensus exercise.[9,10]

Step 1. Selecting the Consensus Method

Figure 1 serves as the entry point to the framework by distinguishing between situations that are better addressed through implicit consensus and those requiring explicit consensus. Questions characterized by scientific novelty, rapidly evolving evidence, or the need for timely interpretive judgment generally favor implicit consensus because they require flexibility rather than formal standardization. In contrast, decisions intended to support regulatory guidance, harmonized standards, policy development, or reproducible regulatory outputs require explicit consensus methodologies that provide structured documentation, predefined procedures, and transparent decision-making.[1,4,6,9,10]

Importantly, Figure 1 does not determine which consensus method should be used; rather, it identifies the appropriate methodological family. This distinction prevents the common misconception that a single consensus methodology, most commonly Delphi, is suitable for every regulatory question. Instead, the figure recognizes that methodological selection begins by identifying the evidentiary and governance requirements of the decision itself.[9,10]

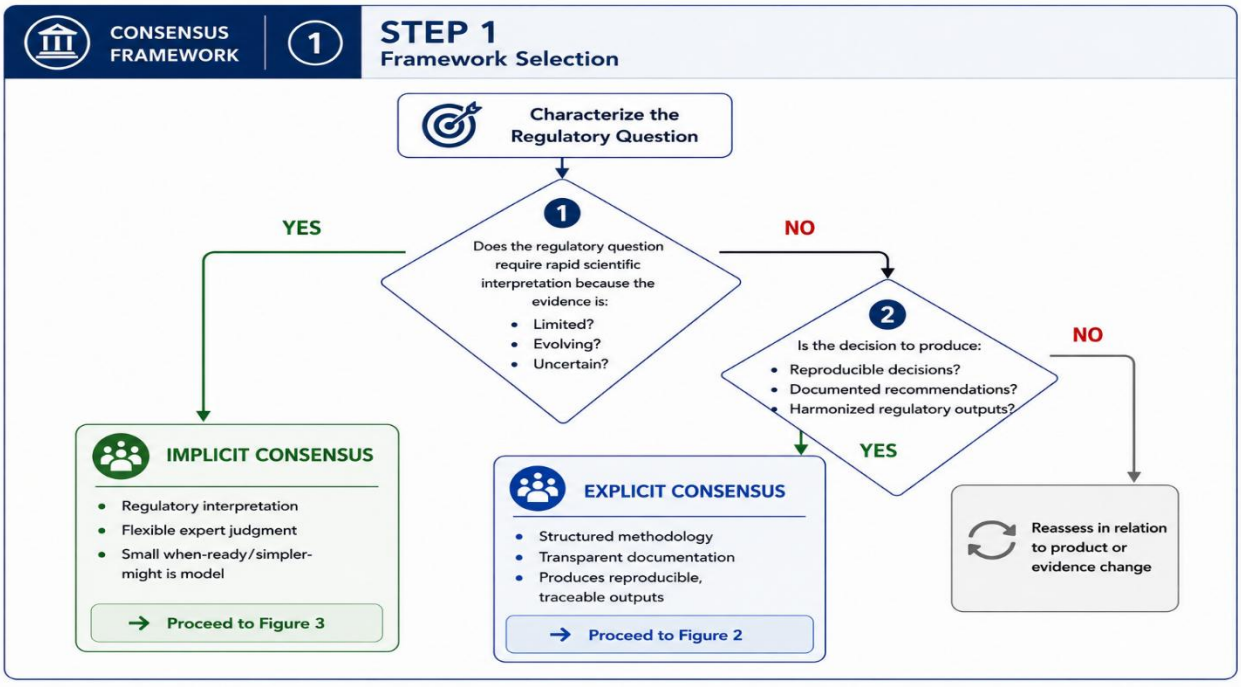

Figure 1. Decision framework for selecting the appropriate consensus method

Step 2. Explicit Consensus Methodologies

Once Figure 1 establishes that explicit consensus is the appropriate methodological family, Figure 2 guides selection of the most appropriate explicit consensus methodology. Rather than recommending a preferred approach, it presents a family of structured methodologies that differ in their objectives, methodological structure, stakeholder engagement, governance requirements, and intended regulatory outputs. The decision tree evaluates these characteristics sequentially, allowing selection of the methodology that best aligns with the regulatory question, evidentiary context, and intended regulatory outcome. Consequently, Figure 2 emphasizes methodological fit rather than methodological preference, recognizing that different regulatory questions require different forms of structured consensus.[9,10]

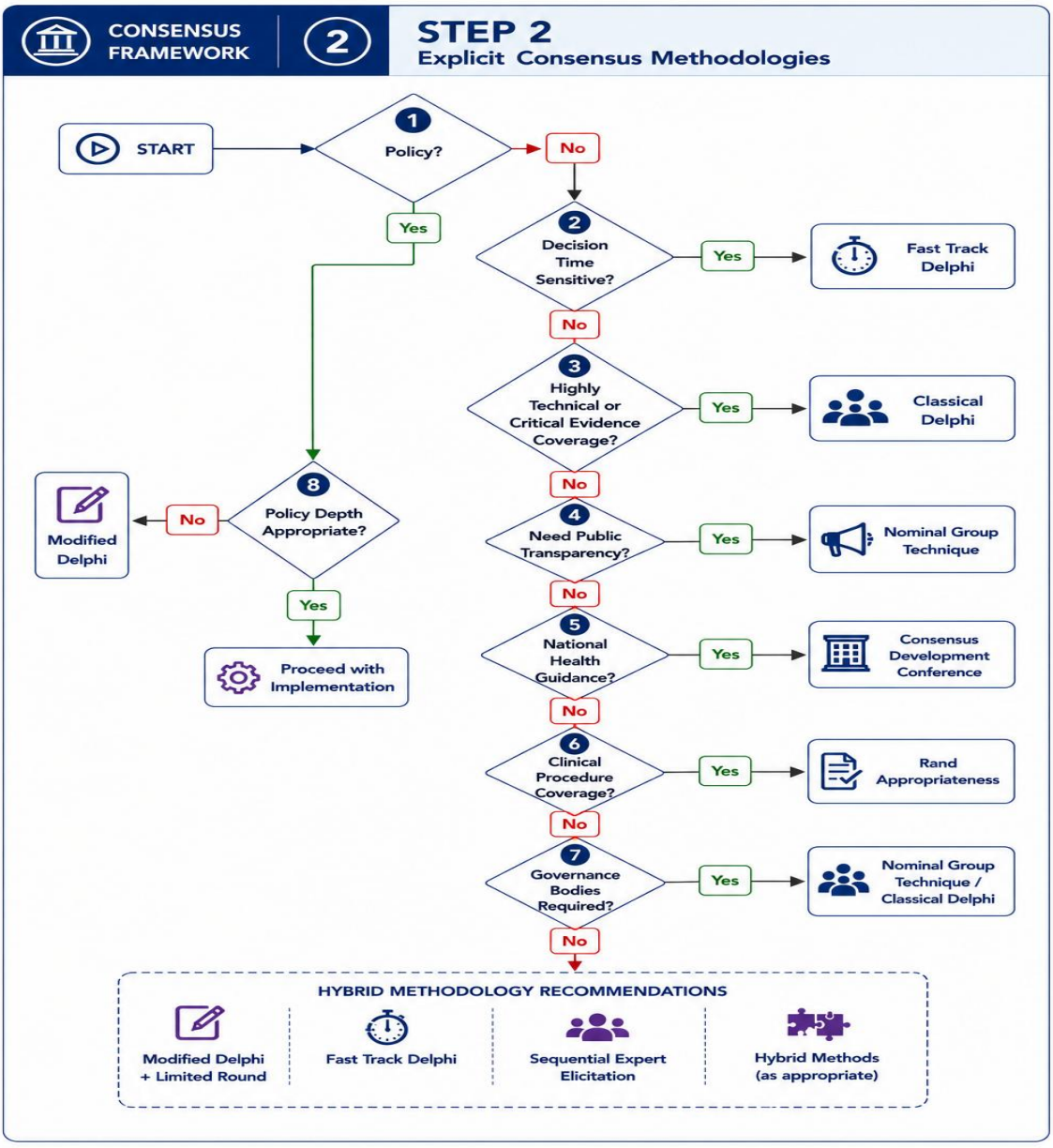

Figure 2. Explicit Consensus Methodologies

Figure 2 concludes with four terminal decision pathways representing explicit consensus methodologies that may be appropriate once the preceding decision criteria have been evaluated. Reaching one of these endpoints does not imply that it is the only acceptable methodology. Rather, it indicates that, based on the sequential decision process, the selected methodology is likely to provide the most appropriate balance between scientific rigor, regulatory objectives, evidentiary uncertainty, and practical implementation. Because several methodologies may be appropriate for closely related regulatory questions, Table 4 provides additional interpretive guidance to clarify the rationale supporting each terminal pathway.

Table 4. Guidance for Selecting Among the Terminal Explicit Consensus Methodologies Identified in Figure 2

Terminal Node	When this endpoint is reached	Why this methodology is appropriate	Alternative if conditions change
Modified Delphi – Limited Round	The regulatory question is well defined, expert agreement is expected, and time is constrained, but structured iteration remains desirable.	Provides efficient consensus while preserving the methodological strengths of Delphi.	Consider Classical Delphi if broader exploration or additional iterative refinement becomes necessary.
Fast-Track Delphi	Regulatory decisions require rapid expert input because of emerging scientific or public health needs.	Prioritizes timely consensus while maintaining a structured and transparent process.	If additional deliberation becomes feasible, a Modified Delphi may provide greater methodological robustness.
Structured Expert Elicitation	Available empirical evidence is insufficient to answer the regulatory question, requiring systematic incorporation of expert judgment.	Explicitly characterizes uncertainty and captures expert knowledge where data are limited.	As additional evidence becomes available, a Delphi-based approach may become more appropriate.
Hybrid Methods	The regulatory question spans multiple scientific or regulatory domains and cannot be adequately addressed by a single consensus methodology.	Combines complementary methodologies to accommodate complex multidisciplinary decision-making.	If the regulatory scope narrows, a single explicit methodology may provide a more efficient consensus process.

Table 4 should be interpreted as an extension of Figure 2 rather than as an independent comparison of consensus methodologies. Whereas the decision tree guides users through the sequential selection process, the table explains the rationale underlying each terminal pathway and highlights circumstances in which an alternative methodology may be more appropriate. Together, Figure 2 and Table 4 demonstrate that selection among explicit consensus methodologies is determined by the characteristics of the regulatory question rather than by preference for a particular technique.[9,10]

Importantly, the terminal pathways are not intended to represent rigid or mutually exclusive decisions. Regulatory questions frequently evolve as additional scientific evidence becomes available, stakeholder perspectives broaden, or regulatory objectives change. Consequently, the framework should be viewed as adaptive, allowing movement between methodologies when warranted while maintaining the principle of methodological proportionality. [9,10]

Step 3. Implicit Consensus Methodologies

Once Figure 1 identifies implicit consensus as the appropriate methodological family, Figure 3 guides selection of the most appropriate implicit consensus methodology. Whereas Figure 2 organizes the structured methodologies available after selection of the explicit consensus family, Figure 3 presents a family of

complementary interpretive methodologies that support regulatory decision-making when evidence is limited, evolving, uncertain, or context dependent. These methodologies differ in their reliance on scientific judgment, professional experience, multidisciplinary deliberation, evidentiary integration, and decision context, reflecting the diversity of regulatory questions encountered during medicinal product development and evaluation. The decision tree evaluates these characteristics sequentially, allowing selection of the methodology that best aligns with the regulatory question, evidentiary context, and intended regulatory objective. Together with Figure 2, it reinforces that methodology selection should remain aligned with the characteristics of the regulatory question, emphasizing methodological fit rather than methodological preference.[8-10]

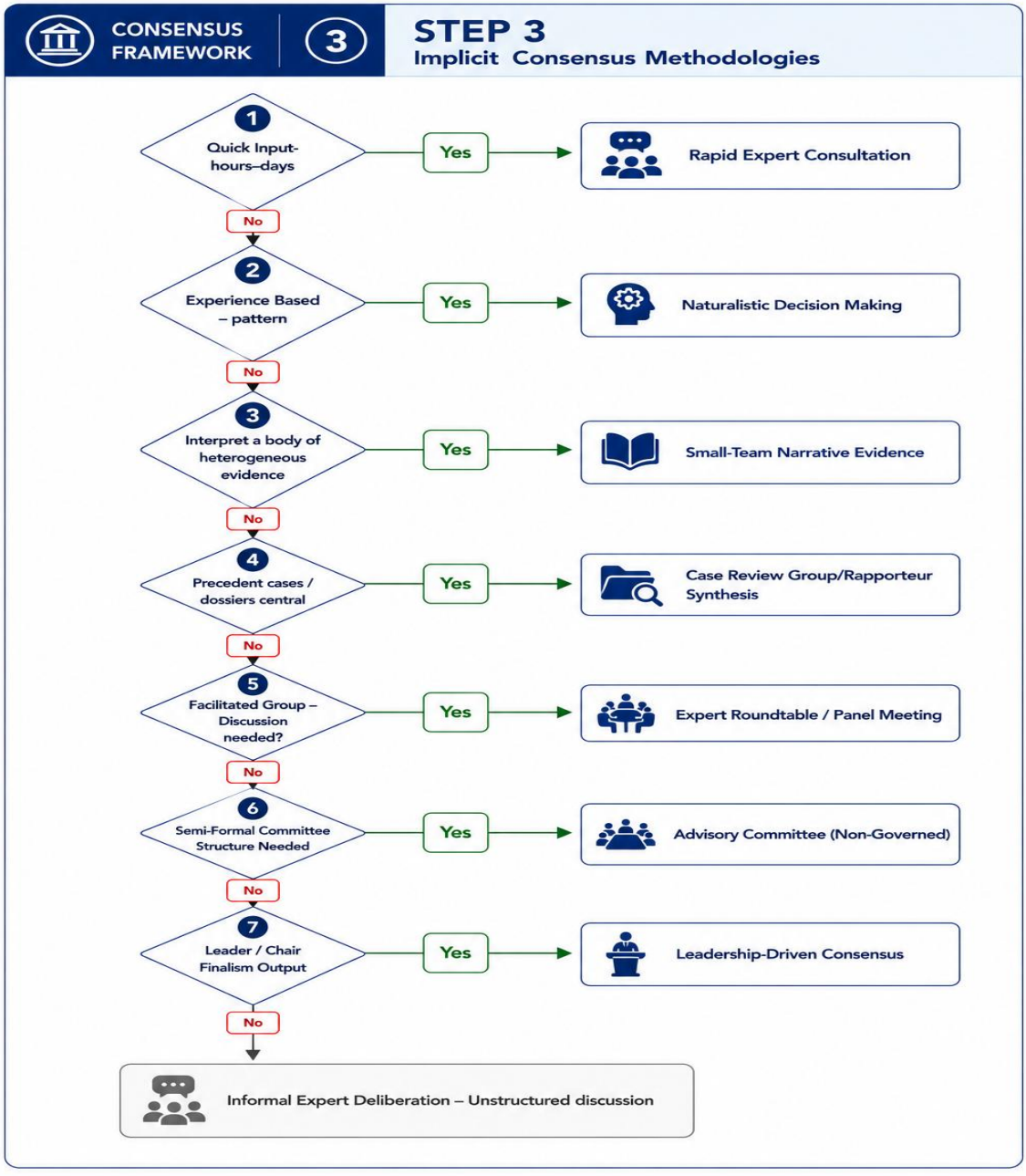

Figure 3. Implicit Consensus Methodologies

Figure 3 should be interpreted as the implicit counterpart to Figure 2 within the framework. Rather than introducing additional methodological choices, it organizes the implicit consensus methodologies discussed in Section 3 into a coherent decision architecture that illustrates their role in regulatory decision-making. Together, Figures 2 and 3 demonstrate that consensus methodology selection begins by identifying the appropriate methodological family and then selecting the approach most consistent with the regulatory question, evidentiary

context, and governance requirements. This organization reinforces the principle that implicit and explicit consensus methodologies are complementary and should be selected according to methodological proportionality.

Step 4. SME Identification and Selection Decision Tree

Once the appropriate consensus methodology has been selected through Figures 1–3, Figure 4 guides the identification and selection of the subject-matter experts (SMEs) or participants required to implement that methodology effectively. Rather than selecting experts before defining the consensus process, the framework aligns participant selection with the methodological, scientific, and governance requirements of the chosen consensus approach. The decision tree sequentially evaluates regulatory experience, subject-matter expertise, conflicts of interest, willingness to participate, and the potential for hierarchical or positional dominance before confirming panel membership. Where potential bias is identified, mitigation strategies such as anonymization or balanced panel composition are incorporated to preserve the integrity of the consensus process. Consequently, Figure 4 reinforces the principle that participant selection should follow methodology selection, ensuring that panel composition remains proportionate to the regulatory question and the objectives of the selected consensus methodology.[9,10,39]

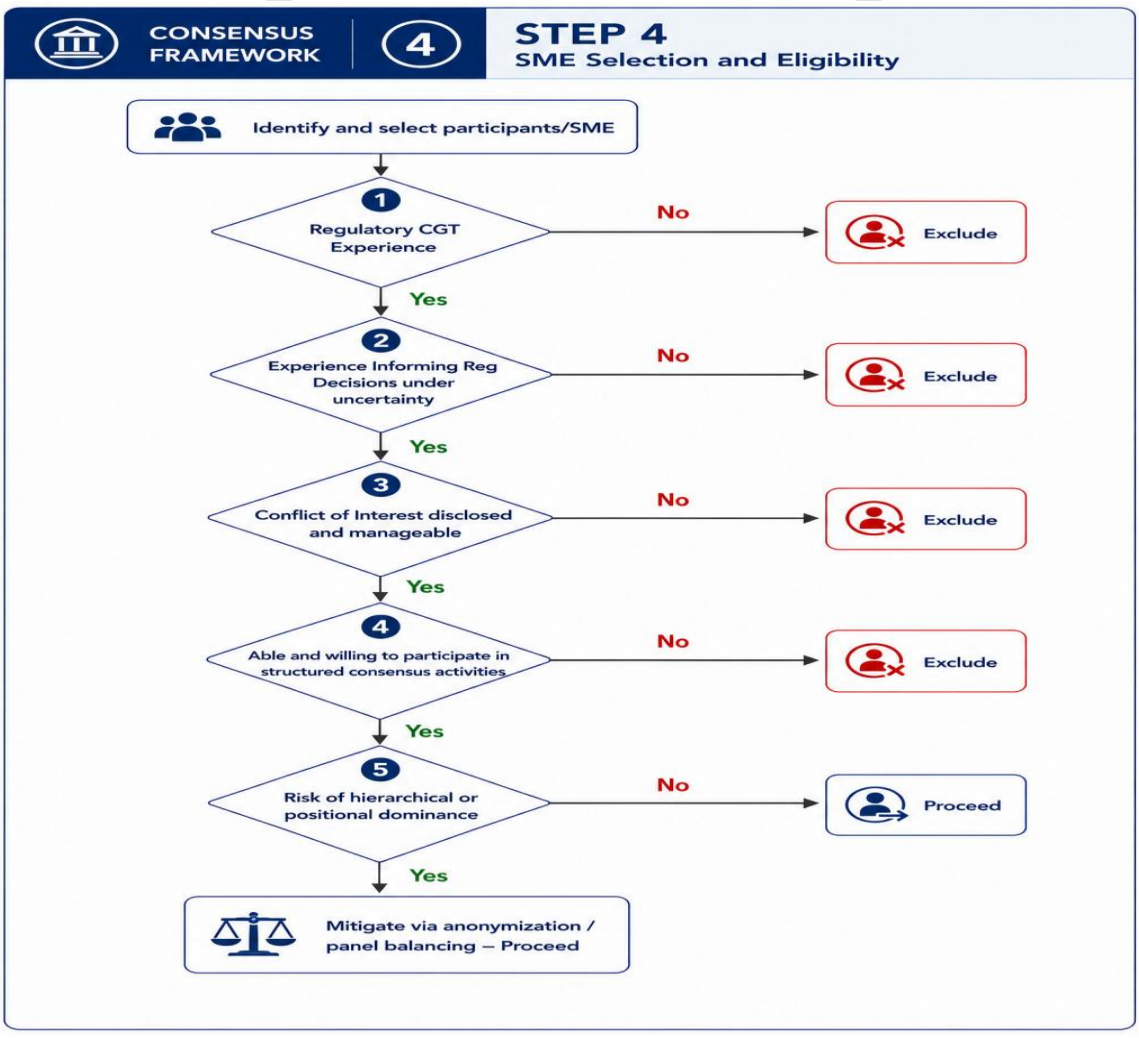

Figure 4. SME and participant selection following consensus method selection.

Figure 4 operationalizes the final stage of the framework by demonstrating that subject-matter expert (SME) selection should occur only after the appropriate consensus methodology has been identified. Different consensus methods require different combinations of scientific expertise, regulatory experience, stakeholder representation, and facilitation. Consequently, participant selection should be driven by the methodological requirements and governance objectives of the selected consensus process rather than by the availability or reputation of individual experts. By aligning panel composition with the consensus methodology, the framework strengthens

transparency, minimizes selection bias, improves reproducibility, and enhances the scientific credibility of the resulting regulatory recommendations.

Integrating the Framework

Taken together, Figures 1 through 4 transform consensus methodology selection from an intuitive or experience-based activity into a structured and reproducible regulatory process. The framework recognizes that consensus design involves a series of interdependent methodological decisions, each informed by the regulatory question, evidentiary context, governance requirements, and intended regulatory use of the resulting recommendations. The final stage of the framework recognizes that different consensus methodologies require different panel compositions. Delphi methodologies generally benefit from geographically distributed experts representing multiple disciplines, whereas the Nominal Group Technique emphasizes balanced stakeholder participation during structured face-to-face discussions. RAND/UCLA Appropriateness Method panels require complementary clinical and methodological expertise to evaluate appropriateness systematically. In contrast, Policy Delphi panels intentionally incorporate diverse scientific, ethical, policy, and patient perspectives to explore competing viewpoints rather than force agreement. Aligning panel composition with methodological requirements improves transparency, minimizes selection bias, strengthens reproducibility, and enhances the credibility of consensus recommendations for regulatory decision-making.[24,33,36,39]

Although developed using cell and gene therapies as the principal case study, the framework is sufficiently flexible to support a broad range of regulatory and health science applications involving scientific uncertainty, multidisciplinary expertise, and transparent decision-making.

Section 7. Application of the Consensus Framework: Developing a Global Harmonized Regulatory Framework for Cell and Gene Therapies

The decision framework presented in the preceding sections provides a structured methodology for selecting consensus approaches according to the characteristics of the regulatory question, evidentiary context, governance requirements, and intended regulatory application. This section demonstrates its practical application to one of the most challenging issues in contemporary regulatory science: the development of a globally harmonized regulatory framework for cell and gene therapies (CGTs). Despite substantial scientific and regulatory advances, differences among international regulatory authorities continue to influence product development, evidence generation, regulatory review, and post-marketing oversight. Applying a structured consensus methodology provides a transparent and reproducible process for identifying areas of agreement, resolving methodological differences, and supporting the development of harmonized regulatory recommendations across jurisdictions.[1,4,6,9]

7.1 Defining the Regulatory Challenge

The globalization of CGT development has created an urgent need for greater international regulatory alignment. Although the FDA, EMA, MHRA, HC, and NMPA share the common objective of ensuring product quality, safety, and efficacy, they continue to differ in regulatory requirements, evidentiary expectations, technical guidance, and post-approval oversight. These differences increase development complexity, contribute to regulatory uncertainty, and may delay global patient access to innovative therapies. As CGTs continue to evolve, the absence of a structured process for developing internationally harmonized regulatory recommendations has become an increasingly important challenge for regulators, industry, healthcare professionals, and patients.[1,4,6,40,41]

The challenge extends beyond scientific or technical considerations. It is fundamentally a question of regulatory science: how can diverse regulatory perspectives be systematically integrated into a transparent, reproducible, and internationally acceptable framework capable of supporting global harmonization while respecting the legal authorities, regulatory responsibilities, and public health priorities of individual jurisdictions? Addressing this question requires more than comparing existing regulatory frameworks; it requires a structured methodology capable of transforming multidisciplinary expert judgment into harmonized regulatory recommendations. The

consensus framework presented in the preceding sections provides one such methodology and serves as the foundation for the case study presented in this section.[9,10,42]

7.2 Application of the Consensus Framework: An Example Protocol

The proposed framework can be applied systematically to guide the selection of an appropriate consensus methodology for developing a globally harmonized regulatory framework for CGTs. The following example illustrates how the decision framework is used in practice.

Question 1. *Is a rapid or standard, structured, reproducible, and harmonized decision required?*

The objective of this study is to establish a unified global regulatory framework for CGTs. Because the intended outcome is a structured, reproducible, and internationally harmonized regulatory recommendation, application of Figure 1 indicates that an explicit consensus methodology is appropriate. The framework therefore proceeds with Figure 2 to determine the most suitable explicit consensus method.[9,10]

Question 2. *Are there any restrictions or constraints that influence methodology selection?*

For this study, the research must be completed within established project timelines and is therefore considered time sensitive. Applying this criterion to Figure 2 identifies the Fast-Track Delphi methodology as the most appropriate explicit consensus method for this research.

Having identified the consensus methodology, the framework proceeds to Figure 4, where the appropriate subject-matter expert (SME) panel is selected. Participant selection is performed only after the methodology has been determined, ensuring that panel composition is aligned with the methodological, scientific, and governance requirements of the selected consensus approach.

Following completion of the methodology and participant selection process, Figure 5 illustrates the operational implementation of the selected consensus methodology. The process includes structured evidence review, expert participation, iterative feedback, consensus development, documentation of decision-making, and generation of the final consensus recommendations. Although illustrated using the Fast-Track Delphi methodology, the operational workflow is readily adaptable to other consensus methodologies by modifying the mechanisms for evidence review, participant interaction, scoring, ranking, or voting while preserving the principles of transparency, methodological rigor, reproducibility, and regulatory accountability. Consequently, the resulting output provides a transparent and reproducible framework for developing globally harmonized regulatory recommendations for cell and gene therapies (CGTs).[14-16,21]

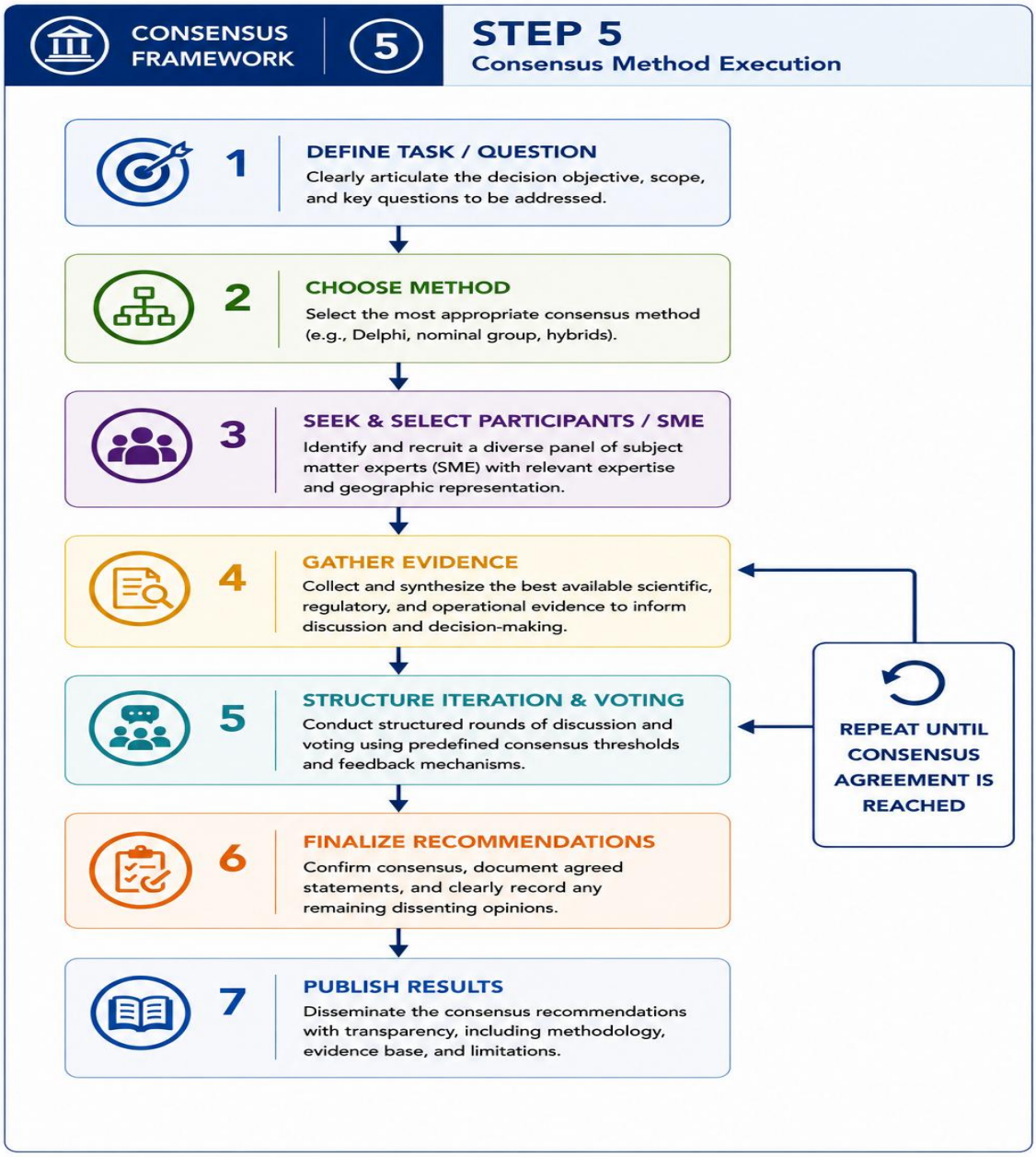

Figure 5. SME consensus selection

In practice, implementation of the selected Fast-Track Delphi methodology would require predefined consensus thresholds, structured digital feedback rounds, systematic documentation of dissenting opinions, and participation by a geographically diverse panel of regulatory and technical experts. These implementation elements help ensure that the consensus process remains transparent, reproducible, and scientifically defensible while supporting development of a globally harmonized regulatory framework for CGTs. [17,21]

Section 8. Discussion

The principal contribution of this article is the introduction of a structured decision framework that positions consensus selection as a regulatory design process rather than a preference-based methodological choice. By separating consensus type identification, methodology selection, and subject-matter expert (SME) selection into sequential stages, the framework aligns methodological structure with the evidentiary, operational, and governance requirements of the regulatory question. This proportional approach is particularly relevant to the regulation of cell and gene therapies (CGTs), where regulatory decisions frequently evolve from an exploratory scientific interpretation towards an increasingly formalized, reproducible, and internationally

harmonized regulatory expectations. This progression reflects the principle of methodological proportionality, whereby the degree of methodological structure should correspond to the characteristics of the regulatory question and the intended regulatory output.[6,9,10]

This distinction reinforces an important principle of regulatory science: different forms of scientific uncertainty require different forms of consensus governance. Implicit and explicit consensus are not competing methodologies but complementary approaches that support different stages of regulatory decision-making. Implicit consensus provides the flexibility needed when scientific novelty, urgency, or limited evidence requires timely multidisciplinary interpretation. Explicit consensus becomes appropriate when decisions are intended to support regulatory guidance, policy development, or internationally harmonized recommendations that require transparency, reproducibility, and auditability. Because CGT regulation frequently progresses from early scientific uncertainty toward standardized regulatory expectations, both forms of consensus are essential throughout the product lifecycle.[8,9,10]

The proposed decision framework therefore represents more than a conceptual model. It provides a practical regulatory design tool that guides consensus methodology selection through a structured sequence of decisions. Figure 1 distinguishes between implicit and explicit consensus according to the characteristics of the regulatory question. Figures 2 and 3 demonstrate that both explicit and implicit consensus comprise multiple methodologies, each designed to address different scientific and regulatory circumstances. Figure 4 reinforces the principle that participant selection should follow methodology selection, thereby aligning panel composition with the objectives and governance requirements of the selected consensus approach. Collectively, these decision trees transform consensus design into a transparent, reproducible, and methodologically defensible process.

The framework also highlights the increasing importance of hybrid consensus methodologies within contemporary regulatory science. Regulatory questions involving CGTs frequently encompass scientific, manufacturing, clinical, ethical, operational, and policy considerations simultaneously, making reliance on a single consensus methodology insufficient in some circumstances. Sequential application of complementary methodologies for example, using the Nominal Group Technique to identify candidate issues, Delphi methodologies to refine consensus, the RAND/UCLA Appropriateness Method to evaluate appropriateness, and Policy Delphi to examine unresolved policy differences allowing methodological rigor to be maintained while accommodating the multidimensional nature of complex regulatory questions.[24,33,36,43]

Several limitations should be acknowledged. Consensus methodologies derive their credibility not only from selecting an appropriate methodology but also from the quality of their implementation. Inadequate participant selection, poorly defined research questions, insufficient facilitation, unclear consensus thresholds, unmanaged conflicts of interest, or inadequate documentation may substantially reduce the credibility and reproducibility of the resulting recommendations. Furthermore, the proposed framework represents a conceptual decision architecture that has not yet been evaluated across multiple regulatory organizations or therapeutic areas. Future research should therefore evaluate its reproducibility, usability, and generalizability through application to real-world regulatory challenges, including endpoint selection, long-term follow-up strategies, manufacturing comparability, benefit-risk assessment, and global regulatory harmonization initiatives.[9,10,39,40]

9. Conclusion

Consensus methodologies function as regulatory governance mechanisms that transform scientific uncertainty into structured, transparent, and actionable regulatory decision-making. Within the regulation of CGTs, this role becomes particularly important because evolving scientific evidence, manufacturing complexity, long-term safety considerations, and rapidly advancing technologies frequently challenge conventional regulatory paradigms. Under these circumstances, consensus extends beyond achieving expert agreement and instead provides a

methodological infrastructure capable of supporting interpretive alignment, transparency, reproducibility, and regulatory harmonization across jurisdictions.[1,4,6,9]

A central contribution of the proposed framework is the principle of methodological proportionality. Consensus methodologies should not be selected according to familiarity, institutional preference, or historical precedent alone. Rather, the degree of methodological structure should be proportionate to the scientific uncertainty, urgency, reproducibility requirements, governance implications, and intended regulatory application associated with the question under consideration. As scientific evidence matures and regulatory expectations evolve, consensus processes may likewise progress from implicit interpretive alignment toward increasingly explicit, structured, and auditable methodologies. This progression enables regulatory systems to preserve scientific flexibility during early innovation while supporting greater consistency, transparency, and public accountability as evidence and regulatory standards mature.[9,10]

Although developed using CGTs as the principal case study, the proposed framework is intended to support a broad range of regulatory and health science applications where multidisciplinary expertise, scientific uncertainty, and transparent governance intersect. Its principal contribution is not the introduction of a new consensus methodology, but a structured decision architecture for selecting the methodology most appropriate to the regulatory question. By aligning consensus methodology with the characteristics of the regulatory question, evidentiary context, governance requirements, and intended regulatory outcomes, the framework provides a transparent, reproducible, and adaptable approach for strengthening regulatory decision-making and supporting greater international harmonization throughout the lifecycle of innovative medicinal products.

Acronym	Definition
ATMP	Advanced Therapy Medicinal Product
CDC	Consensus Development Conference
CGT	Cell and Gene Therapy
CMC	Chemistry, Manufacturing and Controls
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
HC	Health Canada
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
MHRA	Medicines and Healthcare products Regulatory Agency
NGT	Nominal Group Technique
NMPA	National Medical Products Administration
OECD	Organisation for Economic Co-operation and Development
RAM	RAND/UCLA Appropriateness Method
RWD	Real-World Data
SME	Subject-Matter Expert
WHO	World Health Organization

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