

Considerations on the use of reliance in clinical trials review

Introduction

The global clinical trial landscape is undergoing a profound transformation, driven by the increasing use of multiregional clinical trial designs, rapid advances in science and technology, and the growing need for coordinated regulatory approaches. With the expansion of multiregional clinical research, the need for harmonized regulatory frameworks has become more urgent. Despite this shift, regulatory fragmentation—driven by country or region-specific requirements—continues to impede the efficient initiation and conduct of multiregional clinical trials. Such fragmentation delays trial start-up and can diminish the attractiveness of certain jurisdictions for clinical research.

Regulatory reliance, already a well-established practice in regulatory decision-making for marketing authorization and post-approval changes, offers a promising solution. By leveraging assessments conducted by trusted national regulatory authorities (NRAs), reliance mechanisms can reduce duplication, accelerate clinical trial approvals, and promote global collaboration.

Applying the principles of regulatory reliance to clinical trial review is both feasible and necessary to enhance efficiency, uphold the rights, safety, and well-being of trial participants, and foster harmonization.

Scope of regulatory reliance in clinical trials

Clinical trial review encompasses several critical elements:

- Assessment of scientific rationale and study design
- Risk-benefit assessment for participants and safety monitoring plans
- Quality of the investigational medicinal product (IMP)
- Ethical considerations
- Data integrity and reliability of results.

Among these, the methodological evaluation and IMP quality assessment are particularly amenable to reliance mechanisms. These components are typically based on standardized documents such as the Investigator's Brochure (IB), protocol, and quality IMP dossier, which are largely consistent across jurisdictions. Reliance on these shared elements allows NRAs to streamline review processes without compromising scientific rigor or the protection of participants in clinical trials.

Applying reliance principles for ethical reviews presents a more nuanced challenge. While certain ethical principles are universal, others are deeply rooted in local cultural, legal, and societal contexts (e.g. informed consent, data protection, and insurance). Therefore, reliance should be applied selectively to globally consistent ethical aspects, while national ethics committees retain authority over context-specific evaluations. The role of local institutional review boards (IRBs) or ethics committees (ECs) in protecting patients cannot be undermined.

Furthermore, reliance can also extend beyond initial approvals to include clinical trial amendments, ensuring continuity and efficiency throughout the trial lifecycle. Convergence in the categorization of amendments will be essential to support consistent implementation.

Key principles for effective reliance in clinical trial reviews

To ensure reliance mechanisms are both effective and foster trust between clinical trials sponsors and NRAs, implementation should be guided by the following principles¹:



Protect patient safety: Reliance must safeguard the rights, safety, and well-being of those taking part in clinical trials.



Foster trust based on competence: Effective reliance depends on reference NRAs with established regulatory capability and on a clear understanding of roles, responsibilities, review timelines, and expectations. Ongoing dialogue and cooperation further strengthen this mutual trust.



Facilitate transparency: Clear communication on the scope, requirements, process, and limitations of reliance, alongside timely access to relevant information and decisions from reference NRAs, supports predictability. Decisions based on reliance are made transparently, documented clearly, and supported by well-maintained records to ensure accountability, traceability, and confidence in their implementation.



Minimize duplication: Reliance is designed to reduce redundant assessments, thereby improving efficiency, including shorter timelines compared with standard clinical trial application evaluations, without compromising quality.



Uphold quality data standards: Clinical trials must adhere to internationally recognized standards for data integrity, reliability, and robustness (e.g. International Council for Harmonisation (ICH) guidelines).



Respect sovereignty: NRAs retain ultimate decision-making power within their jurisdictions, taking into account ethical considerations, patient population characteristics, and regional factors that may influence trial outcomes.



Support legal alignment: Reliance functions in accordance with national legal and regulatory frameworks. Legal frameworks that enable reliance and allow regulatory guidelines to evolve as needed foster consistent, transparent, and flexible implementation.

Consideration for implementing reliance in clinical trial reviews

To effectively operationalize regulatory reliance in clinical trial review, the following considerations may guide implementation:

Promote convergence with international standards

Align clinical trials requirements with globally recognized standards (e.g. ICH and World Health Organization (WHO) guidelines, Declaration of Helsinki). Greater convergence fosters mutual trust, reduces variability, and simplifies reliance frameworks. Differences in standards or practices, however, do not prevent one NRA from relying on another².

Establish formal agreements when needed

Develop mutual recognition agreements (MRAs) or memoranda of understanding (MoUs) between reference and relying NRAs to facilitate the secure exchange of documentation and enable access to critical, non-public information, while ensuring appropriate handling of sensitive data to protect participant confidentiality. Applying such agreements, where appropriate, strengthens collaboration and supports effective implementation of reliance.

Develop centralized platforms for information sharing

Create secure, centralized digital platforms that facilitate access to assessments and other documentation. These platforms enhance transparency, reduce duplication, and streamline reliance processes, while protecting participant information, ensuring data privacy, and complying with national laws and regulations, particularly in cross-border contexts.

Implement benchmarking tools

Use WHO benchmarking tools^{3,4} for the objective assessment and capacity development of NRAs and ECs to establish a robust and functional approval system. These measures help strengthen trust between countries supporting reliance mechanisms.

Invest in training and capacity building

Provide ongoing training and resources for NRAs, investigators, EC members, and clinical trial staff to ensure consistent understanding and application of reliance principles. Reliance should foster regulatory capacity building, particularly in resource-limited settings.

Pilot reliance models

Test reliance mechanisms in specific therapeutic areas or trial phases. Pilot projects help identify practical challenges, refine processes, and build confidence among all stakeholders before wider implementation.

Engage diverse stakeholder groups

Engage NRAs, ECs, sponsors, patient groups, and other relevant healthcare organizations in planning and implementing reliance. Broad stakeholder engagement promotes transparency, trust, and alignment with the needs of those involved in or affected by clinical research.

Advance equity and informed decision-making

Leverage reliance mechanisms to improve access to demographic and epidemiological data, supporting regulatory decisions that address the needs of diverse populations, including historically underrepresented communities and patients with rare diseases. Such practices contribute to equitable patient access and informed regulatory oversight across jurisdictions.

Embed quality assurance and continuous improvement

Regularly monitor and evaluate the implementation of reliance practices to ensure they are applied consistently and effectively by all staff. Establish key performance indicators for NRAs and IRB/EC to measure functioning and impact of reliance mechanisms. Strengthen existing frameworks and promote timely exchange of information across jurisdictions to foster continuous learning and improvement. Ultimately, the scientific assessment of the content remains the central consideration for applying reliance.

Conclusion

Convergence of clinical trial submission and review processes, along with the adoption of regulatory reliance mechanisms, is essential for streamlining clinical trial operations across regions. These approaches provide tangible benefits, including the potential for more efficient regulatory processes, streamlined global clinical trial application submissions, faster global recruitment, cost savings, and enhanced access to innovative therapies. By embracing reliance, NRAs can remain competitive in the global clinical research landscape while upholding high standards of quality, safety, and ethics. Ultimately, reliance fosters a more collaborative and efficient global clinical trial ecosystem, contributing to faster and more equitable access to new treatments for patients worldwide.

Endnotes

1. The principles are not listed in order of criticality
2. [Technical Report Series, No.1033, Annex 10: Good reliance practices in the regulation of medical products: high level principles and considerations](#), WHO, 2021
3. [WHO Global Benchmarking Tools \(GBT\) for evaluation of national regulatory systems](#)
4. [WHO tool for benchmarking ethics oversight of health-related research involving human participants](#), WHO, 2023



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