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Applications of regulatory precedent research

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Regulatory precedent research plays a crucial role in supporting regulatory science and product development strategies. This article highlights the available tools and approaches for conducting regulatory precedent research and describes their utility to inform decision making in the biotechnology and pharmaceutical industries. Some key applications of precedent research focusing on successful use of real-world evidence (RWE) and external controls are also discussed. The article emphasizes the need for comprehensive evaluation of regulatory precedents, including their limitations and applicability. Understanding and leveraging regulatory precedents can enhance regulatory intelligence, facilitate informed decision making, and contribute to the development of innovative and safe therapeutic products.

Keywords – external controls; postapproval activities; postmarket compliance; precedent research; real-world evidence.

Introduction

Precedent research in drug and biologic regulatory affairs refers to the process of examining and analyzing previous decisions and regulatory actions taken by regulatory authorities, thereby strengthening insight into the present and evolving regulatory landscape and enabling better strategic regulatory decisions. By examining precedents, it is possible to identify trends, common practices, and regulatory expectations that can guide regulatory submissions, decision making, strategy development, and compliance efforts.[1]

Similar to regulatory intelligence, regulatory precedent research analyzes and interprets regulatory information. However, regulatory precedent research focuses on past regulatory decisions to understand legal principles and guide future actions, while regulatory intelligence explores a broader range of regulatory information sources to inform strategic decision making and ensure compliance. Regulatory precedent research is a component of regulatory intelligence, which falls under the broader umbrella of regulatory science.

Precedent research can involve various aspects of drug regulatory affairs, such as drug approvals, labeling requirements, clinical trial design,[2] safety assessments, postmarket surveillance, manufacturing standards, and regulatory enforcement actions. Regulatory guidelines, published regulatory decisions, court rulings, and warning letters also serve as valuable sources of information for analysis. These precedents often reflect the current scientific understanding, risk assessment methodologies, and safety considerations relevant to a particular product or industry.[3]

By studying precedents, pharmaceutical stakeholders (pharmaceutical sponsors, regulatory authorities, R&D organizations, healthcare providers, patients and patient associations, scientists, health insurance providers, and regulatory affairs professionals) can anticipate regulatory outcomes, evaluate the potential challenges and risks associated with regulatory submissions, and develop more practical strategies to ensure compliance with applicable regulations. It can also help in making informed decisions regarding product development, marketing, and postapproval activities.

Definitions

External controls. This is a comparison group that is not part of the clinical trial itself but is used as a reference to evaluate the outcomes and results of the clinical trial. These external controls are typically composed of individuals or data from sources external to the trial being conducted.

Historical data. It is the data collected from previous studies, trials, or research efforts that are used as a reference or baseline for comparison in a current clinical trial.

The role of precedent research

Regulatory strategy formulation

Precedent research supports creation of an effective regulatory strategy for product development. By examining past regulatory decisions and precedents, such as publicly available benefit-risk assessments, companies can identify the regulatory requirements, data expectations, and potential challenges specific to their product type or therapeutic area. This knowledge allows them to design appropriate development plans, anticipate regulatory hurdles, and optimize their regulatory pathway (e.g., new drug application [NDA], abbreviated new drug application, biologics license application). Further, precedents can inform the selection of the optimal pathway based on factors such as the product's characteristics, therapeutic indication, and competitive landscape to maximize the chances of successful approval. By examining similar products or technologies that have been previously approved or rejected, companies can evaluate the regulatory landscape and potential hurdles early in the product development process and assess feasibility.

Supporting regulatory decision making and enhanced predictability

In considering how similar cases have been handled in the past, precedent research allows regulatory authorities to be better equipped to make consistent and informed decisions. As a result, precedent research also enhances the predictability of regulators' decision making. It provides a rationale for establishing regulatory policies, guidelines, and standards that promote safety, efficacy, and quality in the development and approval of drugs and medical products. A deeper understanding of the expectations and requirements of global regulatory agencies will promote transparency and predictability in the regulatory process and enable pharmaceutical companies to anticipate regulatory challenges and align their product development strategies. For example, precedent research can be used to formulate accurate and compliant product labeling and claims. By analyzing precedent cases, companies can understand how regulatory authorities have interpreted and approved labeling content, warnings, precautions, and indications for similar products. This knowledge ensures that the labeling aligns with regulatory standards and effectively communicates the product's benefits and risks to healthcare professionals and patients.[4]

Risk assessment, mitigation, and compliance

The ability to assess and mitigate regulatory risks associated with product development, regulatory submissions, and compliance is essential for successful product launch. By understanding how regulatory agencies have interpreted and enforced past regulatory actions, companies can identify potential areas of concern or noncompliance. This reduces the risk of delays, rejections, or costly postapproval modifications and enables companies to proactively address these issues in their development strategy and to align their operations, manufacturing practices, labeling, and postmarket activities with established standards.

Business planning

Precedent research informs business and investment decisions related to product development by clarifying regulatory precedents and market dynamics, thereby enabling companies to evaluate the commercial viability, competitive landscape, and regulatory hurdles associated with a particular product or therapeutic area. This information guides investment decisions, resource allocation, and business planning.[5]

Regulatory submission preparation

In identifying successful approaches and common pitfalls through precedent research, companies can learn from previous cases regarding the format, content, and level of detail required in regulatory filings and align their submissions accordingly. This knowledge helps to enhance the efficiency of the regulatory review process and reduce the likelihood of requests for additional information or clarification.[1] Understanding how previous submissions have

been reviewed and approved allows companies to tailor their applications and procedures to align with regulatory expectations. Precedent research helps in identifying the types of data, study designs, methodologies, and documentation that have been successful in similar cases, thereby increasing the efficiency of regulatory submissions.

Enabling innovation

Precedent research provides insights into how regulatory agencies have handled novel technologies, therapeutic approaches, or regulatory pathways. It is particularly relevant for advanced therapy medicinal products (ATMPs) seeking to demonstrate comparability to reference products and interchangeability with existing therapies. ATMPs present unique challenges and risks, including safety concerns, manufacturing complexity, and limited clinical experience. Precedent research allows identification of regulatory risks associated with ATMP development and support in optimizing manufacturing processes to align with the regulatory expectations. It facilitates understanding of the evolving regulatory landscape and promotes the development of innovative products by providing a history that can guide the regulatory strategy for new and emerging technologies.[6] Precedent research can help identify accelerated regulatory pathways specifically designed for rare diseases. Regulatory authorities often provide expedited pathways of special consideration for rare diseases to promote faster access to potentially lifesaving treatments.

Study design and data generation

Examination of previous successful submissions and clinical trial registries (e.g., ClinicalTrials.gov and the EU Clinical Trials Regulation) can cultivate greater comprehension of the types of studies, endpoints, patient populations, and statistical analyses that have been accepted by regulatory authorities. This knowledge helps companies design scientifically rigorous studies that align with regulatory expectations and increases the likelihood of generating the necessary data for successful product development.[3] Regulatory policies were recently adjusted to allow for more flexible clinical trial designs during the COVID-19 pandemic. This flexibility includes adaptive trial designs, which allows modification of study protocol in real time based on emerging data. It also allows the acceptance of nontraditional endpoints and surrogate markers to enable quicker predictions of treatment effectiveness.

Postmarket compliance

In learning from past enforcement actions and regulatory decisions, companies can identify potential compliance risks, improve monitoring of adverse events, and ensure postmarket safety surveillance aligns with regulatory expectations. Such precedent research also helps in maintaining compliance with postapproval commitments and addressing any regulatory concerns or inquiries promptly.

Where and how to conduct regulatory precedent research

Online databases

Databases such as PubMed,[7] the WHO Programme for International Drug Monitoring,[8] ClinicalTrials.gov,[9] Drugs@FDA,[10] the European Medicines Agency's European Public Assessment Reports,[11] Health Canada's Drug Product Database,[12] and other country-specific regulatory agency databases can be searched using relevant keywords, product names, or specific regulatory topics of interest.

Literature review

Performing a thorough literature review is essential to identify published articles, research papers, and case studies that delve into regulatory decisions or precedents pertaining to a particular therapeutic area, product type, or regulatory matter. Online databases such as PubMed[7] and Google Scholar[13] offer convenient platforms for searching relevant literature using appropriate keywords. Furthermore, industry publications and regulatory journals can also serve as valuable sources of information for accessing pertinent insights and data.

Case study analysis

Examining published case studies and regulatory analysis reports offers valuable insights into past regulatory decisions and their consequences. These sources provide in-depth information on regulatory hurdles, determinations, and the underlying reasoning. Consulting reports and analyses from regulatory consulting firms, trade associations, and industry experts is also beneficial for comprehending the regulatory environment and precedents within a particular field.

Professional expertise

Harnessing the expertise of regulatory professionals and consultants who specialize in regulatory affairs is instrumental in conducting effective regulatory precedent research. By leveraging their expertise, researchers can benefit from a deeper understanding of regulatory nuances and gain valuable perspectives that enhance the quality and relevance of their regulatory precedent research.

Limitations of regulatory precedent research

Although regulatory precedent research is a valuable tool, it is essential to acknowledge its limitations. The following are some common limitations associated with regulatory precedent research, drawn from the authors' collective general experience.

Contextual specificity

The applicability of regulatory decisions and precedents is often contingent upon the specific regulatory context in which they were established. Various factors, including the therapeutic area, product type, regulatory framework, and

specific case circumstances (e.g., special patient populations), can exert significant influence on their relevance. Racial, ethnic, and cultural factors may also impact regulatory decision making. As a result, it may not be suitable or accurate to directly apply precedents from one jurisdiction or product type to another without considering these contextual factors.

Evolving regulatory landscape

Regulatory policies and guidelines are subject to updates and revisions, rendering precedents potentially outdated or inconsistent with current regulatory standards. Relying solely on precedents may neglect to account for the dynamic nature of regulations and result in misalignment with the latest regulatory expectations. Recognizing this, it is crucial to acknowledge the evolving nature of regulations and incorporate the most recent guidelines and requirements when conducting regulatory precedent research. By doing so, one can ensure compliance with the current regulatory standards and avoid potential gaps or discrepancies.

Variability in interpretation

Regulatory precedents can be susceptible to varying interpretations by different regulatory authorities, which can lead to inconsistencies in decision making. Regulatory agencies may hold divergent perspectives regarding the significance and applicability of past cases, creating challenges in establishing a cohesive regulatory strategy. It is important to recognize these potential variations and navigate them effectively to ensure a consistent approach when dealing with regulatory decisions and precedents.

Scientific advice meetings with concerned regulatory authorities offer a way to obtain validation of the findings from precedent research, clarifying regulatory expectations, identifying additional considerations, assessing regulatory risks, and confirming the benefit-risk assessment. These meetings ensure that the regulatory strategy and trial program are well informed, align with regulatory precedents, and address the specific regulatory requirements and concerns of the authorities. By leveraging scientific advice meetings, developers can further strengthen the application of regulatory precedent research in their product's development and regulatory strategy.

Lack of transparency

Some regulatory precedents may not be publicly available or easily accessible, limiting the ability to conduct comprehensive research and analysis. This can hinder the thorough evaluation of relevant cases and may introduce uncertainty in decision-making processes.

Data limitations

Precedents often rely on historical data, which may have limitations in terms of data quality, completeness, or relevance to current scientific standards. The availability of robust and reliable data is crucial for conducting meaningful regulatory precedent research.

Despite these limitations, regulatory precedent research remains a valuable tool in understanding regulatory expectations and informing drug development strategies. It is important to consider these limitations and supplement regulatory precedent research with other sources of evidence, such as scientific literature, guidance documents, and consultation with regulatory experts (through scientific advice meetings with regulatory agencies), to ensure comprehensive decision making.

Using precedent research

Applying findings from regulatory precedent research can encourage the continued implementation and broader adoption of innovative clinical trial designs, thereby preventing unnecessary delays in the development of treatments for rare diseases. Regulatory approvals based on precedent research typically involve leveraging historical decisions or precedents to support the approval of a new drug.

FDA approval of a new indication based on RWE

The use of real-world data (RWD) to establish clinical evidence regarding the usage, benefits, and potential risks of medical products has emerged as a significant focal point for both industry stakeholders and regulatory authorities. This approach holds the promise of streamlining drug development, lowering costs, and offering deeper insights into actual patient encounters with biomedical products. Recent actions by the FDA signal an expanding reliance on RWE for product approvals. For example, the agency announced in October 2022 a new Advanced Real-World Evidence Program[14] as a Prescription Drug User Fee Act VII commitment to expand opportunities and procedures for sponsors to engage with the FDA on the proposed use of RWE in medical product development. The FDA has also released new guidance relating to the use of RWD and RWE to support regulatory decision making,[15] including clarification of its evidentiary expectations for clinical study designs that use RWD. Moreover, the FDA approved a new indication for Prograf (tacrolimus)[16] based on a noninterventional (observational) study providing fit-for-purpose RWD on effectiveness. This approval has set a precedent in prompting stakeholders to consider the role that RWE can play in various study designs.

Reliance on regulatory precedent for the use of external controls

External controls refer to a comparison group of individuals or patients who are not part of the actual trial but are used as a reference or control group for evaluating the safety, efficacy, or effectiveness of an investigational drug,

medical treatment, or intervention. These external controls provide a basis for comparison with the treatment group or study participants receiving the experimental intervention. The regulatory guidelines established by the FDA mandate the presentation of substantial proof of efficacy through well-designed and adequately controlled trials.[17] Nevertheless, when the use of an internal control is not viable or ethical, especially in the case of rare disease populations, the use of external controls may be deemed an acceptable alternative.

The FDA, in accordance with 21 CFR 314.126[17] and International Council for Harmonisation (ICH) E10 guidance (**Table**), typically acknowledges internally controlled study designs involving concurrent control groups (i.e., placebo, active treatment, dose comparison, or no treatment), where the control and test groups are selected from the same population and treated simultaneously. However, the FDA also recognizes the use of nonconcurrent external controls, which involves comparing outcomes to well-matched historical data, as an acceptable method to provide evidence of effectiveness in certain scenarios. The accompanying table shows examples of ICH and FDA guidance on the use of external controls as comparators in clinical trials, particularly for rare diseases.

Table. ICH and FDA guidance on the use of external controls as comparators in clinical trials

Agency	Guidance title and link	Date
ICH	Choice of control group and related issues in clinical trials – E10	20 July 2000
FDA	Adaptive designs for clinical trials of drugs and biologics	November 2019
FDA	Demonstrating substantial evidence of effectiveness for human drug and biological products [Draft]	December 2019
FDA	Duchenne muscular dystrophy and related dystrophinopathies: Developing drugs for treatment	February 2018
FDA	Expedited programs for regenerative medicine therapies for serious conditions	February 2019
FDA	Expedited programs for serious conditions – Dugs and biologics	May 2014
FDA	Human gene therapy for rare diseases	January 2020
FDA	Interacting with the FDA on complex innovative trial designs for drugs and biological products	December 2020
FDA	Rare diseases: Common issues in drug development [Draft]	February 2019
FDA	Rare diseases: Natural history studies for drug development [Draft]	March 2019
FDA	Use of Bayesian statistics in medical device clinical trials	5 February 2010

FDA, Food and Drug Administration [US]; **ICH,** International Council for Harmonisation.

In the following examples, the sponsors of the identified products obtained regulatory support for using external controls, including retrospective natural history, resulting in product approval. While recognizing the limitations associated with the use of external controls, the FDA consistently took into consideration factors such as the nature and rarity of the condition, the unmet medical need, and the overall body of evidence, including positive secondary or pharmacodynamic endpoints, as well as data from supportive studies. These sponsors both applied prior regulatory precedent research and established new regulatory precedent for reliance upon external historical control data to inform FDA benefit-risk assessment and regulatory action.

Example 1. During an advisory committee meeting, the inclusion of a new indication (monotherapy in patients with partial seizures) for lamotrigine extended-release tablets (Lamictal XR) was supported by historical control data obtained from previously conducted clinical studies. The supplemental NDA relied on a single study that compared 223 patients receiving different dose levels with a historical control group. The historical control group was established through a retrospective analysis of control arms from eight studies previously conducted for other anti-epileptic products.[18] Due to the wealth of control data already available from previous studies, the sponsor deemed the use of placebo or pseudo-placebo controls unethical. At the advisory meeting, the FDA presented a systematic evaluation of key statistical issues based on the Pocock criteria.[19] This evaluation aimed to assess the statistical aspects relevant to the study, considering factors such as study design, endpoint measurements, and analysis methods. The Pocock criteria provided a framework for the evaluation and ensured that the historical control data, derived from similar studies with comparable designs and methodologies, were appropriately analyzed and interpreted. This evidence, including the systematic evaluation by the FDA, played a crucial role in supporting the acceptance of the historical control approach for this specific indication. The use of historical control data from previously conducted clinical studies has provided valuable insights and has subsequently been applied in similar contexts, including the evaluation of other anti-epileptic drugs.

Example 2. The approval of Novoeight, a recombinant antihemophilic factor, for the prophylactic treatment of hemophilia A, a rare disease, is an instance in which historical control data from nine publications were used as external controls.[20] In this case, the annualized bleeding rate (ABR) observed in patients receiving prophylactic treatment with Novoeight was compared to the ABR observed in historical controls who were treated with on-demand regimens. To calculate the historical ABR, data from the nine published studies were weighted based on the number of patients in each study. The mean ABR was determined to be 22 bleeds per patient per year for the historical controls treated with on-demand regimens. By comparison, participants treated with prophylactic Novoeight had a mean ABR of 6.9 bleeds per patient per year,

resulting in a notable 68% reduction in bleeding rate compared to the on-demand therapy historical controls. This significant reduction in bleeding rate observed in participants receiving Novoeight prophylaxis, in comparison to the historical controls receiving on-demand therapy, was deemed acceptable and played a crucial role in the approval of Novoeight for routine prophylactic treatment of hemophilia A.[20]

Overall, the use of regulatory precedent research to understand successful application of RWD and external controls will facilitate continued use and broader application of innovative approaches to clinical trial design while avoiding delays in product development for rare diseases.

New regulatory precedents: COVID-19 vaccine development

The development of COVID-19 vaccines led to the establishment of new regulatory precedents. Regulatory agencies adopted innovative approaches to expedite the approval process and ensure swift public access to vaccines. Conditional approvals, such as the conditional marketing authorization by the EMA, were granted based on promising interim data, employing rolling reviews for the first time and allowing regulatory agencies to continuously assess incoming data and accelerate the review timeline. The new regulatory precedents are discussed in the following items:

- The initial approval of COVID-19 vaccines has played a crucial role in guiding companies to understand the regulatory expectations for these accelerated pathways. This understanding has helped them align their development strategies accordingly, paving the way for subsequent products.[21]

- Regulatory policies have been adjusted to allow for more flexible clinical trial designs during the COVID-19 pandemic. This flexibility includes adaptive trial designs, which enable real-time modifications of study protocols based on emerging data. Nontraditional endpoints and surrogate markers have been accepted to facilitate quicker predictions of treatment effectiveness.[22]

- Robust pharmacovigilance and postmarket surveillance systems have been implemented by regulatory agencies to monitor and assess the safety of vaccines in real-world settings. This enables the timely identification and management of adverse events.[23]

- The urgency of the COVID-19 vaccine development has prompted changes in regulatory procedures, such as an increase in virtual agency meetings, inspections, monitoring, and audits. Regulatory agencies have embraced these innovative approaches to expedite the regulatory approval process, ensuring quicker access to treatments. Eligibility for

accelerated regulatory approval pathways typically requires the potential benefits to outweigh potential risks. Precedent research plays a vital role in identifying the requirements for eligibility and formulating optimal regulatory strategies.[22]

- These regulatory precedents set during the COVID-19 vaccine development have not only facilitated the development and approval of the vaccines but also paved the way for future vaccine development and other medical interventions under similar circumstances. They demonstrate the potential for streamlined and efficient regulatory pathways while upholding rigorous safety and efficacy standards.[22]

Conclusion

Regulatory precedent research is an essential tool for stakeholders to effectively navigate the intricate regulatory landscape in new product development. By drawing on past experiences and insights into the FDA's evidentiary expectations, stakeholders can make informed decisions throughout the product lifecycle, including product development, marketing, and postapproval activities. Using regulatory precedent research to gain a comprehensive understanding of past FDA benefit-risk evaluations, labeling negotiations, and therapeutic-area considerations will facilitate the safe and effective use of drugs and biologics, benefiting patients and advancing public health objectives. Stakeholders should also be aware of the limitations of regulatory precedent research and ensure that other sources of evidence are evaluated to optimize decision making in a dynamic product development program. Such sources may include scientific literature, regulatory guidance documents, and consultation with regulatory experts. By incorporating a variety of information sources, stakeholders can gain a more holistic understanding of the regulatory landscape and make well-informed decisions that prioritize patient safety and public health.

Abbreviations

ABR, annualized bleeding rate; **ATMP,** advanced therapy medicinal product; **EMA,** European Medicines Agency; **FDA,** Food and Drug Administration [US]; **ICH,** International Council for Harmonisation; **NDA,** new drug application; **RWD,** real-world data; **RWE,** real-world evidence; **WHO,** World Health Organization

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References

All references were accessed and/or verified 18 October 2023.

1. Robertson AS, et al. Supporting a data-driven approach to regulatory intelligence. Nat Rev Drug Discov. Published 28 May 2020. https://www.nature.com/articles/d41573-020-00101-4
2. Lim J, et al. Minimizing patient burden through the use of historical subject-level data in innovative confirmatory clinical trials: review of methods and opportunities. Ther Innov Regul Sci. Published 30 December 2018. https://link.springer.com/article/10.1177/2168479018778282
3. Zhang L, et al. A simple approach to incorporating historical control data in clinical trial design and analysis. Stat Biosci. Published 31 March 2022. https://link.springer.com/article/10.1007/s12561-022-09342-w
4. DeMuro CC, et al. Assessment of PRO label claims granted by the FDA as compared to the EMA (2006-2010). Value in Health. Published online 16 October 2013. https://www.sciencedirect.com/science/article/pii/S109830151304237X

5. 21 CFR §60.34, FDA action on petitions. Last updated June 2023. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=60.34
6. Honig P, Zhang L. Regulation and innovation: role of regulatory science in facilitating pharmaceutical innovation [editorial]. Clin Pharmacol Ther. Published April 2019. https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1002/cpt.1367
7. PubMed. https://pubmed.ncbi.nlm.nih.gov/
8. WHO Programme for International Drug Monitoring. https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/networks/pidm#:~:text=The%20WHO%20Programme%20for%20International,any%20other%20drug%2Drelated%20problem
9. ClinicalTrials.gov. https://clinicaltrials.gov/
10. Food and Drug Administration. Drugs@FDA database. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
11. European Medicines Agency. European Public Assessment Reports (EPARs). https://www.ema.europa.eu/en/medicines/what-we-publish-when/european-public-assessment-reports-background-context#:~:text=An%20EPAR%20provides%20public%20information,with%20a%20public%2Dfriendly%20overview.
12. Health Canada. Drug Product Database. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
13. Google Scholar. https://scholar.google.com/
14. Food and Drug Administration. Advancing Real-World Evidence Program. Current as of 25 July 2023. https://www.fda.gov/drugs/development-resources/advancing-real-world-evidence-program#Content
15. Food and Drug Administration. Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products [guidance]. Dated August 2023. https://www.fda.gov/media/171667/download
16. Food and Drug Administration. FDA approves new use of transplant drug based on real-world evidence. Current as of 16 July 2021. https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-new-use-transplant-drug-based-real-world-evidence?utm_medium=email&utm_source=govdelivery
17. Food and Drug Administration. 21 CFR §314.126, Adequate and well-controlled studies. Current as of 7 June 2023. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=314.126#:~:text=314.126%20Adequate%20and%20well%2Dcontrolled,placebo%20effect%2C%20or%20biased%20observation
18. French JA, et al. Historical control monotherapy design in the treatment of epilepsy. Epilepsia. Published 18 June 2010. https://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2010.02650.x
19. Pocock SJ. The combination of randomized and historical controls in clinical trials. J Chronic Dis. Published online 15 April 2004. https://www.sciencedirect.com/science/article/abs/pii/0021968176900448?via%3Dihub
20. Jahanshahi M, et al. The use of external controls in FDA regulatory decision making. Ther Innov Regul Sci. Published online 20 May 2021. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8332598/
21. Leyens L, et al. The COVID-19 pandemic as a catalyst for innovation: a regulatory framework to assess fit-for-purpose innovative approaches in clinical research. Trials. Published online 30 September 2022. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9523630/
22. Kalinke U, et al. Clinical development and approval of COVID-19 vaccines. Expert Rev Vaccines. Published online 14 March 2022. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8935460/
23. Lavertu A, et al. A new era in pharmacovigilance: toward real-world data and digital monitoring. Clin Pharmacol Ther. Published online 28 February 2021. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8058244/