FIFARMA

ADOPTION OF NOVEL CLINICAL
EVIDENTIARY STANDARDS
FOR REGULATORY
DECISION-MAKING FOR
APPROVALS IN **LATIN AMERICA:**

FIFARMA CONCEPT PAPER

Contents

(1.0) **INTRODUCTION**

The landscape of drug development is evolving, and both Health Authorities and Industry are facing unique challenges, as well as opportunities to bring innovative medicines and treatments to patients more quickly. In this context, the unprecedented pace of advances being made in the field of regulatory science is of particular importance.

To modernize drug development, improve efficiency and promote innovation, international reference regulatory authorities – such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) – have focused on advancing novel evidentiary standards to accelerate patient access to new medicines and improve the efficiency and success rates of clinical trials across a range of therapeutic areas with unmet medical needs.

These efforts include modernization of clinical research via the use of innovative and complex trial designs, leveraging real-world data/real-world evidence (RWD/RWE) from clinical practice to inform regulatory decisions on the benefit–risk balance for efficacy and safety, and the approval of drugs through accelerated pathways based on a surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict clinical benefit, complemented by additional post-approval evidence generation.

FIFARMA believes it is important to increase awareness among regulatory agencies in the Latin America region of the different types of evidence from clinical trials and observational studies that can be used to inform regulatory decisions, particularly with respect to the novel regulatory mechanisms mentioned.

Benefits of adopting novel clinical evidentiary standards

The adoption of novel clinical evidentiary standards for regulatory decision-making can have several benefits.

- Earlier approval enables quicker access to safe and effective new drugs that treat serious or life-threatening conditions for which the risks associated with delayed or no treatment have negative consequences, such as oncology indications.

- Modernization and the use of alternative designs increases the effectiveness of clinical trials to provide high quality data to support regulatory and reimbursement decision making, and may allow for more ethical study designs (e.g. the potential to assign fewer people to receive a placebo control).

- Use of RWE to supplement data obtained from clinical trials provides important information about patient populations seen in the real-world setting, which may provide a more accurate depiction of the use of treatments in patients. There is the potential to use RWD more effectively to support medicinal product development and use. Examples include long-term follow-up to confirm life-changing benefits and risk reduction; identification and confirmation of opportunities for precision medicine; and providing context and control groups for assessments in rare diseases.

The following sections discuss these interconnected topics in more detail: the role of innovative and complex trial designs, RWD/RWE, and expedited approvals based on surrogate endpoints. Challenges around the use and acceptance of these approaches in Latin America are highlighted, together with recommendations for how issues can be addressed.

2.0 INNOVATIVE AND COMPLEX CLINICAL TRIAL DESIGN

Defining the situation

Innovative and complex clinical trial design approaches have altered some of the paradigms of randomized controlled trials (RCTs) that have been established over the last seven decades. Therefore, developing and applying innovative and complex clinical trial methodologies is not without its challenges. These novel clinical initiatives use unique approaches to obtaining evidence, which require an open mind, knowledge, and flexible thinking from regulators, in order to manage the scope and impact of these types of studies on the decision-making process.

Given the rapid pace of innovation globally, and the generally slower access to innovative medicines in Latin America, a "fit-for-purpose" flexible approach to clinical trial design methodology is encouraged in the region. At present, innovative and complex clinical trial design approaches are applicable in some countries only. For the benefit of all healthcare stakeholders, Latin America regulatory authorities should aim to foster and include innovative clinical trial approaches within their regulatory framework, regulations, and guidelines.

What do we mean by innovative design?

Any trial design that differs from the standard RCT design and delivers results more efficiently, reduces the study timeline and maximizes the knowledge gained could be considered novel or innovative. Among reference regulatory authorities there are some minor differences in how such approaches are classified; however, the principles are the same. Overall, innovative clinical trial design approaches can be classified as: [CBER Dec 2020, CTFG Feb 2019, NIHR, CTFG Feb 2019, Nass et al. 2018, EFPIA Mar 2020, Gandhi]

- Adaptive
- Master protocol (Basket, Umbrella, Platform)
- Pick-a-winner

- Dose-ranging
- Targeted or stratified
- Bayesian

BOX 1

Innovative and complex clinical trial designs: glossary

Adaptive trial: Allows for the modification of trial design elements during the trial, based on data collected during the trial [Park et al. 2018, Cerqueira et al. 2020]. Many different adaptive designs are possible; examples of elements that may be adapted include randomization schemes, sample size, treatment arms, doses/regimens and endpoints.

Master protocol: A unifying study design that allows simultaneous evaluation of more than one investigational drug and/or more than one disease [Bogin 2020]. Types of master protocols include:

- **Basket:** evaluates one therapy in multiple patient populations (e.g. with different types of cancer).

- **Umbrella:** evaluates multiple therapies (or combinations of therapies) for a single disease.

- **Platform (adaptive platform trial):** evaluates multiple therapies for a single disease, with each therapy allowed to exit or enter according to a decision algorithm that allows adaptations to the trial based on data generated earlier in the trial [Bogin 2020].

Pick-a-winner: Designed to select the most promising treatment to undergo further evaluation amongst multiple potential therapies/schedules. Inferior therapies are eliminated, treatment arms can be modified, and additional arms can be added, based on interim analyses [Mandrekar & Sargent 2006, Cerqueira et al. 2020].

Bayesian approach: Uses predictive probabilities. The prior belief about the effects of an intervention is expressed as a probability distribution (prior distribution) which is updated as data accumulates (posterior distribution). In adaptive trials, the posterior distribution is used to assess the probability of outcomes of interest occurring if the trial continues with the same design, which can be used to decide whether adaptations should be made [Park et al. 2018].

Current landscape

Worldwide, several regulatory authorities accepted as WHO reference regulatory authorities, including the US Food and Drug Administration (FDA), European Medicines Agency (EMA), the UK Medicines and Healthcare products Regulatory Agency (MHRA), the Australian Therapeutic Goods Administration (TGA), and Health Canada, already consider data from innovative and complex clinical trial designs within the regulatory decision process for products used to treat oncological disorders or rare diseases, unmet medical needs, and other types of life-threatening conditions. These agencies have frameworks, regulations, or guidelines which facilitate the use of innovative clinical trial design for product development and regulatory decision making [EMA Nov 2019, CBER Dec 2020, Health Canada Feb 2022, CTFG Feb 2019, NIHR, CTFG Feb 2019, Thomasson 2020].

Likewise, global organizations such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the WHO endorse and support the use of innovative and complex clinical trial methodologies. ICH has developed a concept paper titled "E20: Adaptive Clinical Trials" [ICH Nov 2019] and the WHO has published a position statement aimed at supporting therapeutic developments for tuberculosis by highlighting key clinical trial characteristics and approaches to advance novel therapies for this disease [WHO 2021b].

Another important factor providing first-hand motivation for regulatory authorities to alter their mindset and thinking around this type of evidence has been the COVID pandemic.[1]

In the Latin America region, where innovative and complex clinical trial design approaches have not yet been fully accepted, change is needed, to help deliver innovative medicines to patients. A clinical environment must be encouraged that supports the many therapeutic areas where drug development does not follow the traditional pathway described in current regulations and clinical standards for trials in the region. We need to focus our attention on how the traditional clinical development paradigm has evolved to include "seamless drug development", where the phases described in clinical standards for trials documents have been replaced by other approaches, which allow accelerated drug development in fields such as Oncology. This also includes the use of RWD [Thomasson 2020, Nass et al. 2018].

Defining the challenge around innovative/complex trial design

Although innovative and complex clinical trial design encompasses several different approaches and different product types, there is currently uncertainty around the acceptability and applicability of this type of trial design in certain contexts, such as the strength of the evidence generated by innovative or complex designs from the perspective of regulators and Health Technology Assessment bodies.

These uncertainties are driven by unresolved questions concerning evidence thresholds for aspects such as error rates, feasibility studies, and acceptable methodologies for very small patient populations. These issues can be explained and managed appropriately provided the information, reports and analyses accompanying studies are clear, and provided stakeholders receive the skills training needed to understand the details that are useful for decision making.

Challenges in Latin America

Several key challenges related to the use and acceptance of innovative and complex trial designs in Latin America have been identified.

- Regulatory frameworks, regulations and/or guidelines for the use of innovative clinical trials in regulatory decision-making processes are still evolving.

- Clinical trial submission process is complex and is not predictable.

- Lack of full awareness and understanding of such designs, resulting in complex methodological evaluations.

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[1] Dr Kirsty Wudenbach, Deputy Manager of the Clinical trials unit at MHRA, has commented: "The emergence of COVID-19 also highlighted the need for greater flexibility around novel trial designs, an area that MHRA was already heavily involved with before the pandemic".

FIFARMA recommendations for the use and acceptance of innovative and complex trial designs

The following recommendations from FIFARMA are aimed at addressing the challenges around the use of innovative and complex trial designs in Latin America.

- Improve awareness and build capability through training and seminars.

- Promote harmonization and adherence to international standards and guidelines [EFPIA Apr 2020].

- Ensure current clinical trial regulations do not hinder or prevent the advancement of innovative designs.

- Adopt a pragmatic approach and suitable regulatory environment for innovative and complex clinical trials.

- Implement abridged regulatory pathways, whereby a regulatory decision is solely or partially based on a regulatory reliance application [EFPIA Apr 2020].

- Acknowledging the limited capacity and resources available to evaluate innovative and complex clinical trials, regulatory authorities should utilize reliance mechanisms:

  - Reliance approach [WHO 2021a, WHO 2021c, FIFARMA Sep 2021] whereby a regulatory authority takes into account an assessment of complex clinical trials by a reference regulatory authority or trusted institution, and performs an abbreviated review focusing on the applicability of the results to the local population and healthcare system.

  - Recognition approach (unilateral or mutual) [WHO 2021a, WHO 2021c], whereby a regulatory authority accepts the regulatory decision of a reference regulatory authority or trusted institution whose regulatory requirements are deemed sufficient to meet the regulatory requirements of the reliant authority.

- Advance global coordination around the topic, for example via ICH deliberation on complex clinical trials.

(3.0) USE AND ACCEPTANCE OF RWD/RWE FOR REGULATORY DECISIONS

Defining the situation

The growing availability of electronic health records and other electronic patient-level data (including social media, apps, claims data, and registry data) — collectively referred to as "real world data (RWD)," "big data," or "real life data" — is leading to the increased use of such data to support pharmaceutical development. This is achieved through use of appropriate real-world study designs and methodologies, known as real world evidence (RWE). The US FDA defines RWE as "clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD" and indicates that "RWE can be generated by different study designs or analyses, including but not limited to, randomized trials, including large simple trials, pragmatic trials, and observational studies (prospective and/or retrospective)" [FDA May 2019]. EFPIA definitions of RWD/RWE are provided in Box 2.

FIFARMA believes that RWE can improve medical disease management and health outcomes by providing patients and healthcare professionals with information that helps them select the most appropriate and effective therapies for a specific medical condition.

RWE can also be used by regulatory agencies when they make regulatory decisions about the safety and effectiveness of medical products.

FIFARMA believes that the acceptance of new strategies that facilitate the approval of novel health technologies in Latin America is necessary to increase patients' access to innovative therapies that improve their quality of life. One trend for generating scientific support for the safety, quality and efficacy of medicines is the increasing use of RWD/RWE as part of the "totality of evidence" [FDA Jan 2009]. This phrase reflects the nature of drug development, with each successive piece of data building on prior data to provide the quantity and quality of evidence needed to adequately assess risks and benefits.

RWD/RWE information can be valuable to support regulatory decision-making around the world and therefore it is necessary to align regulatory and scientific concepts and recommendations in this regard.

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BOX 2

EFPIA definitions of real-world data and real-world evidence [EFPIA Aug 2021]

Real-world data (RWD): an umbrella term for data regarding the effects of disease (patient characteristics, clinical and economic outcomes; health related quality of life) and health interventions (e.g., safety, effectiveness, resource use) that have not been collected through highly controlled randomized controlled trials (RCTs). Instead, RWD can either be primary research data collected in a manner which reflects how interventions would be used in routine clinical practice or secondary research data derived from routinely collected data. RWD therefore, refers to the source of raw information. Both paper and electronic records are sources of RWD: including clinical notes, electronic health records (EHR) and medical records (EMR), insurance claims, patient registries, records of patient reported outcomes / experiences, and continuous patient monitoring data (e.g., from apps and wearables). It is possible to collect RWD in a study or trial following an initial intervention when the design is pragmatic.

Real-world evidence (RWE): evidence created by addressing specific research questions through the scientific analysis of RWD rather than from conventional highly controlled RCTs.

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Current landscape

There are several ongoing initiatives by regulatory authorities worldwide focused on the development of RWD/RWE best practice and on frameworks to facilitate the generation of high-quality evidence (i.e. reliable and relevant data [FDA Dec 2018]) to facilitate regulatory decision-making (Table 1) [EFPIA Aug 2021]. Some of the main examples include the EMA Regulatory Science Strategy to 2025 [EMA Mar 2020] which incorporates recommendations from the HMA-EMA Joint Big Data Task Force [HMA/EMA Feb 2019]; the FDA's RWE Framework [FDA Dec 2018] and the recently announced Advancing RWE Program (which provides an optional pathway for early discussion of proposed RWE studies) [FDA Oct 2022]; the Health Canada-CADTH-INESS RWE framework [Health Canada Apr 2019]; China's NMPA RWE project [NMPA Jan 2020]; and Japan's Medical Information Database Network (MID-NET) [PMDA Oct 2019]. Consequently, researchers, developers, and healthcare decision-makers (such as regulators, health technology assessment bodies, and payers) are now using evidence and insights from RWD in a variety of ways [EFPIA Aug 2021].

The use of RWD/RWE will evolve hand-in-hand with technological developments and will depend on the available information sources and their objectives. It will require the establishment of trust with regulators with respect to the relevance and reliability of such evidence to support drug safety and efficacy assessments. There are currently many challenges associated with the use and acceptance of RWD/RWE for regulatory decision-making, including: fitness of data (data must be carefully assessed and validated to determine if it is fit for regulatory purposes); granularity and quality of the information; analysis methodology; and security and protection of the information. FIFARMA believes it is desirable to develop consistent guidance across countries in the Latin America region, which should take into consideration, and align with, international guidelines and recommendations. Dissemination of knowledge and best practices is also necessary.

TABLE 1

Key existing RWD/RWE guidance initiatives outside the Latin America region

Organization	Guidance
European Medicines Agency (EMA)	• EMA regulatory science to 2025 - strategic reflection [EMA Mar 2020] • Guideline on registry-based studies [EMA Oct 2021]
Heads of Medicines Agencies–European Medicines Agency (joint) (HMA-EMA)	• Priority recommendations of the HMA-EMA joint Big Data Task Force [HMA/EMA Feb 2019] • Big Data Steering Group – workplan 2021–2023 [HMA-EMA Aug 2021]
US Food and Drug Administration (FDA)	• Evidence-based review system for the scientific evaluation of health claims – guidance for industry [FDA Jan 2009] • Framework for FDA's real-world evidence program [FDA Dec 2018] • Submitting documents using real-world data and real-world evidence to FDA for drugs and biologics – guidance for industry [FDA May 2019]

	• Considerations for the use of real-world data and real-world evidence to support regulatory decision-making for drug and biological products – draft guidance for Industry [FDA Dec 2021] • Real-world data: assessing electronic health records and medical claims data to support regulatory decision-making for drug and biological products – guidance for industry [FDA Sep 2021] • Data standards for drug and biological product submissions containing real-world data – draft guidance for industry [FDA Oct 2021] • Real-world data: assessing registries to support regulatory decision-making for drug and biological products guidance for industry – draft guidance [FDA Nov 2021] • Advancing real-world evidence program [FDA Oct 2022]
Chinese National Medical Products Administration (NMPA)	• Guidelines for real-world evidence to support drug development and review (interim) [NMPA Jan 2020]
Japanese Pharmaceuticals & Medical Devices Agency (PDMA)	• PMDA's initiative on real world data utilization for regulatory purposes [PMDA Oct 2019]
UK Medicines & Healthcare Products Regulatory Agency (MHRA)	• MHRA draft guidance on randomised controlled trials generating real-world evidence to support regulatory decisions [MHRA Dec 2021]
Health Canada	• Optimizing the use of real world evidence to inform regulatory decision-making [Health Canada Apr 2019]

FIFARMA recommendations for the use and acceptance of real-world evidence in Latin America

Given the advancements within science, including the use of RWD/RWE to support regulatory making decisions, regulatory authorities face increasing challenges with respect to the implementation of efficient regulatory mechanisms to support the quality, safety, and efficacy of medicines. All stakeholders have already begun work on the adoption of regulatory mechanisms including convergence, harmonization, and acceleration in the context of emergency approvals, a process which has been accelerated by the COVID-19 pandemic [ICMRA May 2022].

Acceptance of RWE for regulatory decision-making

FIFARMA believes that there are significant opportunities for enhancing the acceptance of RWE to support regulatory decision-making in Latin America.

- Reinforce the use of reliance mechanisms [FIFARMA Sep 2021].

  - In cases where approval in a country is based on the approval of a reference country (reliance) that involves RWD/RWE, it is recommended to consider such approval, since the reference regulatory agency will have assessed, evaluated and approved the RWE.
  - The reliant agency could rely on the reference agency's overall assessment, and perform an abbreviated review focusing on the applicability of the results to the local population and healthcare system, with consideration of ethnic factors where appropriate. This recommendation aligns with the 2021 WHO Good Reliance Practice document [WHO 2021a] and the ICH E5(R1) Ethnic Factors guideline [ICH Feb 1998].
  - Use of RWD/RWE to evaluate ethnic differences between regions, for example to support the concept of a pooled region or subpopulations, would optimize implementation of the ICH E17 Multi-Regional Clinical Trial Guideline [ICH Dec 2017].

- Partnerships between the Latin American regulatory authorities and stakeholders is essential to foster increased understanding of RWD/RWE, as well as the challenges and gaps that need to be addressed, in order to develop adequate standards that enable RWE to be used more effectively.

- Explain the importance of addressing the challenges in availability and speed of data in a landscape that is rapidly evolving (Health Authority engagement, workshops).

- Use RWD/RWE to supplement single-arm clinical trials, when RCT are not feasible or ethical (e.g., rare diseases, pediatric and/or oncology drug development, targeted populations).

Promoting regulatory convergence on standards for RWE generation

The RWD/RWE framework proposed by FIFARMA for the Latin America region includes promoting regulatory convergence on standards for evidence generation through collaborative action and partnership between industry, regulatory agencies and other relevant stakeholders to achieve the following.

- Establish a clear and "single" definition of RWD/RWE in alignment with international guidelines from regulatory agencies.

- Promote the use and acceptance of RWD/RWE to support benefit/risk decision-making, including technical guidance documents and case studies, while also considering transparency in the use of these data.

    - Generation of high-quality evidence, data extrapolation/representativeness for the local population (to "allow" the use of foreign data), and analysis to underpin healthcare decision-making.
    - Transparency with respect to how RWD/RWE has helped in decision making, how data have been generated, and the source of the data.

- Promote early communication and alignment between the National Regulatory Authorities and the Marketing Authorization Holder/sponsors about RWD/RWE to reinforce the importance of having all stakeholders aligned.

- Promote use of RWD/RWE across a product lifecycle, including new drug applications as well as indication extensions and post-approval requirements.

- Show the importance of using RWD/RWE for orphan drugs, geriatric populations, and underserved populations such as pediatrics.

- Promote use of RWD/RWE in the context of a product safety profile.

- RWD/RWE can supplement or augment RCTs, serve as a bridge to local data, and, as part of the totality of evidence support regulatory decision-making and allow new medicinal products to be made available to patients and for public health [EFPIA Aug 2021].

General considerations for policies concerning RWD/RWE

Given that appropriate tools and methods for fit-for-purpose, high quality RWD generation are often unavailable in Latin America, FIFARMA also makes the following general recommendations.

- Develop policies that would support robust healthcare data infrastructure and the capture of high-quality RWD.

- Investment into better data capture across the region, given the importance of the quality of RWD for use in decision making.

Collaboration between organizations

In addition to regulatory authorities, data generators (e.g. registry holders, data vendors) should be involved in discussions about RWD best practice, given that sponsors must rely on them for data. Collaboration between organizations can help in several ways.

- Facilitate opportunities for early engagement during development.

- Discuss specific local requirements.

- Ensure the correct availability of resources, capacity, and experience for support during product development.

- Increase multi-stakeholders' awareness and capabilities related to the use of RWE, by defining actions to ensure that there is a clear understanding of the expectations for data quality, including data collection and handling.

- Expand knowledge and share best practices.

- Consider establishing an RWE pilot program through which the agency and sponsors could gather insights and publicly share lessons learned.

- Cross-border data sharing where appropriate.

4.0 SURROGATE ENDPOINTS AND ACCELERATED REGULATORY APPROVAL

Defining the situation

For some years, reference Health Regulatory Authorities such as the FDA, EMA, Health Canada and PDMA, have recognized the necessity for the faster introduction of novel therapies. For that reason, they have fostered and applied regulations to accelerate drug regulatory reviews, to ensure that drugs for unmet medical needs and life-threatening conditions are available to patients. These actions have been taken while maintaining high standards for assessments and requiring close follow-up of approved medicines, in order to guarantee the quality, safety, and efficacy of approved products.

Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval. For effectiveness, the standard is substantial evidence based on adequate and well-controlled clinical investigations. For safety, the standard is having sufficient information to determine whether the drug is safe for use under conditions prescribed, recommended, or suggested in the proposed labeling. Under accelerated approval, regulatory bodies such as the FDA may rely on a particular kind of evidence, such as a drug's effect on a surrogate endpoint, as the basis for approval [FDA May 2014]. Such evidence is carefully evaluated to ensure that any remaining doubts about the relationship between the effect on the surrogate endpoint and clinical benefit are resolved by additional post-approval studies or trials (Box 3). An application for accelerated approval should include evidence that a proposed surrogate endpoint or an intermediate clinical endpoint is reasonably likely to predict the intended clinical benefit of a drug [FDA May 2014].

An additional consideration for diseases that can be present in different stages, such as cancer, is that clinical studies evaluating safety and efficacy must take account of both the disease being treated and the stage of disease. This may be relevant for the selection of surrogate or intermediate clinical endpoints.

Current landscape

According to the FDA, a surrogate endpoint is defined as "a clinical trial endpoint used as a substitute for a direct measure of how a patient feels, functions, or survives" [FDA Jul 2018].

From a regulatory perspective, there are three types of surrogate endpoints, based on their level of clinical validation [FDA May 2014].

- **Validated surrogate endpoints,** which are used to support standard approvals.

- **Reasonably likely surrogate endpoints,** which are reasonably likely to predict clinical benefit and can be used to support accelerated approvals.

- **Candidate surrogate endpoints,** which provide exploratory information and remain investigational.

The use of surrogate endpoints can accelerate drug development and considerably shorten the time required to grant regulatory approval, which allows patients faster access to promising new medicines. Medicines approved based on surrogate endpoints are typically granted an accelerated approval that is contingent upon the sponsor's continuing research, involving Phase 4 studies, or confirmatory studies, which are required to verify the efficacy and long-term safety of the drug (Box 3).

BOX 3

Confirmatory studies

Confirmatory studies are performed in late-stage drug development to confirm therapeutic efficacy seen in early-phase clinical trials [NCI, EMA Jan 2019]. The EMA indicates that such trials should provide robust evidence of efficacy in a broad patient population [EMA Jan 2019].

If a drug is approved via an accelerated pathway, based on a surrogate endpoint, post-marketing confirmatory studies are required to verify its clinical benefit [NCI, FDA May 2014].

The FDA indicates that such trials(s) should be underway at the time the application for approval is made, or, if it is not clear that approval will be based on a surrogate endpoint until shortly before or after the submission, then the design and conduct of the confirmatory study should be agreed before marketing approval is granted [FDA May 2014].

Surrogate endpoints support applications in diverse diseases and areas of treatment, most notably:

- Oncology/hematology, where better treatment options are extending patients' survival and drug development is increasingly moving to the early stages of disease, e.g. (neo)adjuvant therapy

- Long-term diseases, such as hepatitis C, HIV, and cardiovascular disease

- Rare diseases, unmet medical needs, and advanced therapies.

Some examples of surrogate endpoints with their correlative relevant clinical endpoint are provided in Table 2 [FDA May 2014]. Additional examples of approvals granted based on the use of surrogate endpoints can be found in the list posted on the FDA website (CDER Drug and Biologic Accelerated Approvals Based on a Surrogate Endpoint) [CDER Jun 2022]. The FDA also publishes a table of surrogate endpoints that may be considered for development programs [FDA Feb 2022].

TABLE 2

Examples of surrogate endpoints used to support FDA accelerated approval [FDA May 2014]

Surrogate endpoint	Clinical endpoint
HIV viral load	Irreversible morbidity or mortality
Radiographic evidence of tumor shrinkage	Overall survival
Laboratory test showing clearance of bacteria from bloodstream	Clinical resolution of infection

When are surrogate endpoints useful?

The main situations where it may be appropriate to use surrogate endpoints are summarized below [FINH Jul 2018, Ciani et al. 2017].

- When conventional clinical outcome assessments require a very long period of observation (e.g. 10–20 years), such as the evaluation of cognitive function and cancer therapies.

- Where the use of surrogate endpoints reduces the duration of clinical trials, which translates into faster introduction of the new medication or therapy to the market (without adversely affecting safety or efficacy), bringing advantages to patients and to physicians making treatment decisions.

- When it is not feasible to measure the true disease outcome directly; for example, when brain biopsies would be needed, which are only feasible post-mortem.

- When clinical outcomes of interest might take a very long time to develop/occur, such as strokes.

- When clinical outcomes may be influenced by other diseases or treatments administrated concomitantly.

- In situations where conducting a clinical endpoint study would be unethical.

In a general sense, a surrogate outcome will only be a good representative of the real outcome if the surrogate endpoint itself is the sole or a major contributor to the progression of the disease/disorder towards the real clinical endpoint.

An approach involving surrogate endpoints will only be acceptable if the benefit outweighs the risks to patients [FINH Jul 2018]. This is most likely to occur in the setting of serious diseases and/or those with a high unmet medical need.

Advantages of using surrogate endpoints

There are several key benefits associated with the use of surrogate endpoints in clinical trials.

- More rapid introduction of innovative therapies for serious, life-threatening diseases, such as cancer, and for rare diseases.

- Reference regulatory authorities are willing to grant accelerated approvals based on evidence from surrogate endpoints/intermediate clinical endpoints that are considered reasonably likely to predict the intended clinical benefit of a drug (with the proviso that confirmatory studies are undertaken to corroborate the clinical benefits); Latin America authorities can take advantage of this existing scrutiny via regulatory reliance procedures [FIFARMA Sep 2021].

Role of stakeholders

Success with respect to the acceptance of an approach involving surrogate endpoints requires multidisciplinary cooperation between stakeholders (e.g. academia, industry, government, non-governmental organizations), and must include an assessment of the risk-benefit balance for the proposed strategy.

Regulatory authorities play a critical role in enabling patient access to therapeutic products for unmet medical needs by adopting expedited pathways and risk-benefit approaches to allow for faster approvals. As seen, the use of surrogate endpoints in clinical trials can facilitate faster drug development. Major reference regulatory authorities such as the FDA and EMA approve some new drugs based on surrogate endpoints, and other regulatory authorities can use reliance mechanisms to speed up the approval of such drugs in their region [WHO 2021a, FIFARMA Sep 2021].

(5.0) CONCLUDING REMARKS

FIFARMA makes the following general recommendations for the use and acceptance of novel regulatory mechanisms by Latin America regulatory authorities.

- Aligned and science-driven global regulatory standards provide assurance of quality, safety and efficacy, and can foster the generation of robust scientific data through various mechanisms to support timely access to innovative and effective medicinal products.

- Efficient regulatory pathways are equally important, to enable good decision-making and optimal use of agency and industry resources, to facilitate delivery of treatments to patients.

- When a Latin America regulatory authority is considering a medicinal product that addresses an unmet medical need, and which has already been approved by another authority based on a development process that involves novel regulatory tools and mechanisms (innovative and complex trial design, RWD/RWE, surrogate endpoints), the regulatory reliance principles emphasized by the World Health Organization (WHO) [WHO 2021a] and the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) [IFPMA 2019] should be applied, in order to expedite the approval and speed up the availability of the new medicine to local patients.

- It is recommended that regulatory authorities that are willing to establish a regulatory framework fostering the use of innovative and complex trial designs, RWD/RWE and surrogate endpoints should provide early engagement opportunities during the medicinal product development and review process. This will facilitate discussion of any specific local requirements. Such a framework could also increase awareness and capabilities among multiple stakeholders, through educational training, collaboration and knowledge sharing.

- Regulatory authorities should ensure that the adoption of any novel regulatory mechanisms respects data privacy concerns and provides accountability to patients.

While there are certainly challenges ahead, scientific advancements have brought us to a time of great opportunity. These opportunities should be seized, not only for the benefit of people who currently depend on safe and effective medicines, but for those waiting for breakthroughs to come, and for all future patients.

With this in mind, FIFARMA aims to collaborate with regulatory authorities to establish regulatory mechanisms regarding the acceptance and application of innovative and complex clinical trial designs, RWD/RWE, and surrogate endpoints, to ensure alignment with international bodies and reference regulatory authorities in other regions. FIFARMA invites regulatory authorities to share their views and progress regarding the acceptance of these approaches for regulatory decision-making.

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