European Federation of Pharmaceutical Industries and Associations

# An EFPIA position paper on randomised pragmatic trials to generate high-quality real-world evidence for regulatory decisions

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## 1. Executive summary

Currently, the traditional randomised, controlled clinical trial (RCT) is the gold standard for providing robust evidence to support an evaluation of efficacy and safety leading to registration of a molecule. In the future, we anticipate that the traditional RCT will only provide a portion of the total evidence for a medicine over its lifecycle (Eichler et al. 2021 [1]) and that effectiveness data from real-world evidence (RWE) will play an increasingly important role in complementing available efficacy evidence for future regulatory submissions.

Randomised pragmatic trials (RPT), which leverage real-world data (RWD) sources, offer an opportunity to generate fit-for-purpose RWE, i.e. the right data at the right time for the right scientific question and purpose. This paper (a) defines the type of pragmatic trials with the highest potential to generate RWE to inform regulatory decision making; (b) outlines opportunities and advantages for patients, healthcare providers, regulators and drug developers; (c) reviews considerations in designing RPTs and identifies potential challenges; and (d) recommends actions to enhance the utility of RPT in the European Union (EU).

RPTs offer an opportunity to address the needs of multiple stakeholders: For patients and healthcare providers, the burden of visits and procedures is reduced as they are mostly aligned with routine clinical practice; for regulators, RPTs provide evidence applicable to the “real patient” while randomization ensures internal validity. RPTs could also address drug developers’ needs, e.g. by accelerating patient recruitment (opportunity to recruit patients beyond “traditional” investigational sites) and by simplifying trials by focusing on the collection of fit-for-purpose data variables thereby increasing the efficiency and feasibility of studies.

The concept of pragmatic trials is not new (Schwartz and Lellouch 1967 [2]), but only a few RPTs generated evidence for regulatory decisions. Uncertainty on the acceptability of key RPT design elements (e.g. on real-world endpoints, fit-for-purpose data quality, simplified procedures, and informed consent) render the design and execution of RPTs for regulatory decision-making challenging. Considering all ongoing EU and international efforts to improve the utility of RWD (e.g. the development of relevant regulatory guidance, ‘’fit-for-purpose principles’’ on data quality considerations), there is now an opportunity to collectively explore and address challenges related to the use of pragmatic trials to generate high-quality RWE for regulatory decision. This also aligns with the European Medicines Agency (EMA) goal of transforming the design and conduct of trials in the EU by, amongst other means, facilitating the use of novel designs and/or methodology, under the Accelerating Clinical Trials (ACT) EU initiative [3].

In summary, EFPIA considers that in certain situations (i.e. for the appropriate scientific question and regulatory intent) the use of carefully designed RPTs can be an additional tool in drug development. RPTs that include fit-for-purpose considerations (e.g. on data and methods) can result in the generation of RWE in support of regulatory decisions. We recommend several actions (**Table 2**) to build on the momentum in the ongoing RWD efforts, which include raising greater awareness of this type of studies and their potential value, addressing operational challenges, and increasing their regulatory acceptance and utility. For this purpose, EFPIA proposes a more in-depth analysis of some of the operational and regulatory challenges, e.g. through EMA- workshop to discuss some of these challenges, as well as the creation of a pre-competitive consortium to work on demonstration projects collaboratively with other stakeholders (e.g., patient organizations, investigators, regulators, and drug developers).

## 2. Introduction

EFPIA acknowledges that the traditional RCT is the current gold standard for providing robust evidence to support an evaluation of efficacy and safety leading to the registration of a medicinal product. In the future, we anticipate that the traditional RCT will provide only a portion of the total evidence for a medicine over its lifecycle (Eichler et al. 2021 [1]) and that effectiveness data will play an increasingly important role in complementing available efficacy evidence. Considering the European vision of establishing the value of RWE for regulatory decision making by 2025 (Arlett et al. 2022 [4]), EFPIA evaluated the role and value of pragmatic clinical trial designs that leverage RWD sources in generating high-quality evidence for regulatory decisions.

RWD is generally defined as ''*routinely collected data relating to patient health status or the delivery of health care from a variety of sources other than traditional clinical trials*'' (Arlett 2020 [5]) although exact definitions vary amongst countries/regions. Such sources include electronic health care records (EHR), registries, and administrative claims (e.g. medical, pharmacy) databases. Performing studies and analyses from data such as EHR and registries that are already collected during routine clinical practice could therefore generate RWE. The prospect of randomisation, ''pragmatism'' (e.g. collecting a few high-quality variables), and pre-specification of analyses makes pragmatic clinical trials another important drug development study design that, when applied in the right regulatory and clinical context, can generate high-quality RWE for regulatory decisions.

Despite the existence of pragmatic trials for several decades, only a few of these studies have contributed evidence for regulatory decisions. The EMA Scientific guidance on post-authorisation efficacy studies [6] describes pragmatic trials as:

> *''Pragmatic trials examine interventions under circumstances that approach real-world practice, with more heterogeneous patient populations, possibly less-standardized treatment protocols and delivery in routine clinical settings as opposed to a research environment. Minimal or no restrictions may be placed on modifying dose, dosing regimens, co-therapies or co-morbidities or treatment switching."*

The degree of pragmatism in different domains (e.g. eligibility, type/extent of data collection) within a pragmatic trial will depend on the objectives of the trial and how the results will be used (see Section 3).

Pragmatic trials can be conducted as randomised or non-randomised studies, but for regulatory decision-making, it is recommended to use a robust randomisation process (EMA [6]). For that reason, this paper focuses on RPTs.

While there are specific challenges in the conduct of RPTs (see Section 7), the following considerations have prompted EFPIA to assess the value of RPTs in contributing evidence for regulatory decisions when used in the appropriate regulatory and clinical context:

- Efforts (in the EU and globally) to support the generation of high-quality RWD (e.g. standardized format to minimize variability in data collection) and RWE
- The prospect of generating evidence from randomized designs resulting in treatment effects where confounding by baseline measured and unmeasured characteristics is minimised
- Pragmatic trials promote patient-centricity through increased focus on collecting patient-relevant outcomes while lowering the burden on participants (e.g. less visits).
- Collecting data from the "real patient'" (i.e. a more inclusive and diverse patient population increasing the external validity [generalizability] of the study results)

- Enable participation of patients in clinical trials that would normally not have access to the traditional clinical sites (e.g. because they live far away)
- Possibility to simplify the conduct of clinical trials and accelerate drug development
- The advancement of digital technologies such as digital health technologies (DHT), which facilitate the collection of objective, longitudinal data directly from patients

## 3. Scope and possible uses of RPTs

A recent publication by Concato and Corrigan-Curay (2022 [7]) describes clinical trial designs with increasing reliance on RWD. For example, on one end of the spectrum, a traditional randomised trial (explanatory trial; for definition see Appendix 10.1) leverages RWD to inform the design, while on the other end of the spectrum, a non-randomised, non-interventional study completely relies on RWD to generate RWE. RPTs are located in between these extremes and somewhat closer to the traditional RCTs due to the randomized and interventional nature, but they directly leverage RWD sources. Given the current EU regulatory and healthcare landscape and depending on the objective of the study, EFPIA is of the opinion that RPTs with the following features may offer the greatest opportunity to generate high-quality RWE to inform regulatory decision-making as well as patient and physician treatment decisions in the immediate future:

- Randomised interventional trials that are embedded in clinical practice settings (for definition of clinical practice see Regulation (EU) No. 536/2014 Q&A [8] and Appendix 10.1) and
- Include pragmatic elements (e.g. data collection time points as in the real world) and
- Leverage RWD data sources (e.g. EHRs) and
- Are conducted with authorised medicines (i.e. available evidence in other indications) and, in exceptional cases, with new medicinal products.

The degree of pragmatism will depend on the objectives of the trial and how the results will be used (e.g. to support regulatory decisions). The Pragmatic Explanatory Continuum Indicator Summary-2 (PRECIS-2 tool; Loudon et al. 2015 [9]) has been developed to match trial design decisions to the intended use of the results. The PRECIS-2 wheel measures the degree of pragmatism in nine domains (eligibility, recruitment, setting, organization, flexibility: delivery, flexibility: adherence, follow-up, primary outcome, and primary analysis) using a 5-point Likert scale for each domain (from 1=very explanatory to 5=very pragmatic).

**Possible regulatory and clinical settings appropriate for the use of RPTs**

The scientific objective and regulatory intent are key drivers in determining the study design. Examples of possible regulatory and clinical settings in which RPTs could be advantageously used to generate RWE are listed below.

Regulatory settings (i.e. type of regulatory decisions)

- Approval of new indications for a product with an established safety profile (i.e. post-authorisation)
- Provide evidence (safety or effectiveness) for post-authorisation measures (PAMs) - for example, could be part of the confirmatory strategy for a medicinal product which received conditional approval.
- In exceptional situations (e.g. outstanding benefit with high-quality data in an unmet medical need setting) for marketing authorization of a new medicinal product

Clinical situations/settings that could be amenable to the conduct of RPTs

- Trials in which a large effect size is anticipated based on previous evidence (e.g. clinical studies in another indication) ensuring sufficient statistical power despite larger heterogeneity in pragmatic trials (e.g. due to broader population, more variability in compliance to treatment and/or treatment switches)
- Trials with outcomes/endpoints of importance to patients and providers, measured in routine clinical practice in a generally consistent and reliable way to limit assessment bias
- Disease settings that require limited interventions within routine clinical practice (e.g. limited blood sample collection)
- Trials to provide evidence that a medicinal product is effective across diverse clinical settings (e.g. late-stage cancer to earlier lines)
- Settings where long-term follow-up or capture of treatment adherence is needed
- Situations where exploratory data collection (e.g. additional biomarker data not directly linked to the primary objective of the study) is not of interest
- Clinical settings where the collection of RWD is less likely to lead to major quality and/or completeness gaps. Examples include:
- Missing data (e.g. on comorbidities, labs, prognostic factors, and outcomes) can be adequately addressed
- Situations where a blinded study is not (or at least less) required or feasible
- Settings where RWD interoperability is enabled, i.e. ability for systems and data formats to interact with each other
- Disease areas or populations where
  (a) it is difficult to recruit a sufficient number of patients (e.g. rare diseases or paediatrics)
  (b) high-quality data systems (e.g., registries) are available, or
  (c) comparison needs to be performed against multiple agents or evolving standard of care (SOC)

Examples of scientific questions addressed through the conduct of RPTs

- The medicinal product(s) are already authorised in some types of cancer and will be compared to the SOC in new indications; e.g. the Pragmatica-Lung cancer trial (SWOG-S2302; [10]; Clinical Trials.gov NCT05633602)
- For urgent new treatments when access to a large number of patients is imperative (e.g. for COVID-19 and the related RECOVERY study (Normand 2021 [11]; RECOVERY web page [12]; ClinicalTrials.gov NCT04381936).

For additional examples, see Appendix 10.2.

## 4. Landscape analysis

Multiple EU and international guidelines and initiatives aiming to facilitate the use of RWD/RWE are currently underway or completed. This section provides a non-exhaustive list of such efforts, including the generation of RWE and efforts to embed clinical research in clinical practice (see **Table 1**); international initiatives and guidance are listed in Appendix 10.3.

**Table 1 Initiatives and guidance**

| |
|---|
| **EU regulatory guidelines** |
| ✱ Guideline on registry-based studies (22 October 2021) EMA/426390/2021 [13]<br>✱ Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies (9 October 2017) EMA/813938/2011 Rev 3* [14]<br>✱ Scientific guidance on post-authorisation efficacy studies (12 October 2016) EMA/PDCO/CAT/CMDh/PRAC/CHMP/261500/2015 [6]<br>✱ Draft Data Quality Framework for EU medicines regulation (Released 10 October 2022) [15]<br>✱ ENCePP Guide on Methodological Standards in Pharmacoepidemiology, Rev 10 (30 June 2022) [16]<br>✱ HAS France: Real-world studies for the assessment of medicinal products and medical devices (10 June 2022) [17] |
| **EU health policy initiatives/coalitions** |
| ✱ Several European Commission-EFPIA public private partnership projects under the Innovative Health Initiative (IHI [18]) (previously Innovative Medicines Initiative [IMI]), including impactful outcomes such as the creation of the GetReal Institute [19] and the GetReal Initiative [20].<br>✱ EuroHeart [21]: A collaboration between the European Society of cardiology and national registry holders that, in part, will facilitate the conduct of registry-based RCTs (Wallentin et al. 2019 [22]). |
| **Tools** |
| ✱ The PRECIS-2 tool: designing trials that are fit for purpose (Loudon et al. 2015 [9])<br>✱ GetReal RWE Navigator: Introduction to generating, understanding, and using RWE; Study design: Pragmatic trial [23]<br>✱ GetReal Trial Tool; Navigating RWE options in clinical trials [24] |

## 5. Opportunities for stakeholders

Below we outline what makes RPTs attractive to various stakeholders (e.g. patients, healthcare professionals, regulators and drug developers).

**Patients and healthcare providers**

- Reduced **burden** on patients and investigational sites/investigators compared to a traditional clinical study (e.g. visits and procedures mostly aligned with routine clinical practice, patients receive treatment at their usual point of care, data access via EHRs as opposed to study-specific case report forms)
- Broader patient **access:** Increased opportunity to participate in clinical trials as patients receive treatment at their usual point of care, and therefore RPTs may facilitate enrollment of a more diverse patient population (e.g. race, ethnicity, age, sex, comorbidities)
- Increased **confidence** that the results from RPT are applicable to the **broader patient population**: Eligibility criteria are generally broader in RPTs than the typically more restrictive criteria in a traditional RCT.
- Randomisation between two or more available therapeutic options may allow **comparison with several existing alternative treatments** and give recommendations on which one(s) to use in that clinical context
- **Patient-centricity:**
  - RPTs are more likely to use **endpoints** measured in routine clinical practice and that are more meaningful to patients and the overall public health.

- Enable more patient-centric longitudinal **data collection**; leverage new technologies (e.g. data generated from Digital Health Technologies [DHTs] including those used routinely by patients [e.g. Smartphones] to collect outcomes important for patients, e.g. heart rate and PROs, to facilitate drug development and minimize burden of data collection)
- Generation of evidence to inform treatment decisions and the **adoption** of an intervention in clinical practice

**Regulators**

- Generation of fit-for-purpose, high-quality RWE to inform regulatory decisions (e.g. enable a label update, especially when it concerns efficacy/effectiveness claims)
- Incorporation of randomisation to minimize confounding and thus reduce bias (increase internal validity)
- Generation of evidence that more closely reflects how a broader patient population is cared for in routine clinical practice by relying on RWD sources instead of extensive prescriptive protocol data collection and time points
- Contribution to international efforts on the consistent use of RWD (e.g. leveraging data from EHRs) from different types of centres (e.g. academic, small community practice, point of care) and the generation of informed regulatory guidelines

**Drug Developers**

- Can **close evidence gaps** for scientific questions that are not addressed via a traditional clinical trial
- **Accelerate patient recruitment (and ultimately drug development)** due to design specificities; opportunity to recruit patients beyond "traditional" investigational sites (e.g. community practice, point of care)
- Increase **efficiency** of studies through the use of RWD sources

## 6. Key considerations related to the conduct of RPTs

This section outlines key considerations related to outcomes and endpoints, statistical methods, operational and regulatory aspects that are of particular relevance to the conduct of RPTs. As for any study with regulatory intent, a protocol with pre-specified endpoints, methods, statistical analyses, ethics approval, compliance with Good Clinical Practice, and pre-registration is key to increase regulatory acceptability. Delineating and discussing these elements early with regulators can enhance the opportunity for the study results to be considered relevant for regulatory decisions.

**Endpoints and outcomes**

While objective clinical outcomes (measured variable) and endpoints (analysed parameter) commonly utilized in traditional RCTs may also be relevant to real-world practice (e.g. mortality) and reduce the potential for bias in data collection and reporting, selecting outcomes important to patients and their healthcare providers to inform effectiveness is essential (Loudon et al. 2015 [9]). However, aligning outcomes and endpoints important to patients and providers in real-world practice and those important to regulators may present even greater challenges than in RCTs.

- **Clinical trial endpoints:** For example, progression-free survival (PFS) is a surrogate endpoint for overall survival (OS) used in traditional RCTs for oncology interventions that is widely recognized and accepted by health authorities for regulatory applications. However, PFS in clinical trials uses Response Evaluation Criteria in Solid Tumors (RECIST) criteria for evaluation, whereas in real-world practice, RECIST measurements of progression are often not feasible. In certain instances, real-world PFS (rwPFS or rwP) using information abstracted from secondary data sources such as

EHR databases and documents (e.g. clinician notes) may provide important insights and therefore supportive evidence that reflects the patient's journey during routine clinical care (Torres et al. 2022 [25], Griffith et al. 2019 [26]).

- **Patient-/provider-centric endpoints and outcomes:** For example, patient-reported endpoints/outcomes that may be primarily used for provider decision-making regarding treatment or disease management in the real-world setting may be subject to increased scrutiny and may require additional data to increase confidence of regulators for acceptance in regulatory decision-making. This could be due to several factors including but not limited to perceived (or real) subjectivity in the endpoint measurement, lack of validation against "hard" clinical endpoints or endpoints measured in traditional RCTs, and/or limited capacity for standardisation. Subjective endpoints (e.g. Patient Reported Outcomes [PROs]), while potentially more prone to bias, may be more relevant for patients and a key component for provider decision-making during routine care; thus, such endpoints are more likely to be included in RPTs.
- **Digital Health Technologies:** The use of DHTs to capture clinical information and outcomes is increasing, particularly for assessments in neurologic (e.g. Alzheimer's Disease, Parkinson's Disease), respiratory (e.g. asthma, chronic obstructive pulmonary disease [COPD]), or metabolic conditions (e.g. diabetes). Additionally, biometric assessments and PROs in multiple other diseases are increasingly utilised. Collection of digitally derived outcomes may provide ease for patients and providers and a capacity for enhanced completeness of relevant, real-time, real-world data.

As with efficacy parameters, pragmatic **safety reporting** is an important consideration in the design and conduct of RPTs when taking the EU pharmacovigilance system into consideration; however, meeting regulatory requirements for monitoring and reporting can be challenging in this setting. Examples of topics that will need to be determined and discussed with regulators include what is a reportable event and whether reporting should be limited to e.g. Serious Adverse Events and Adverse Events of Special Interest. Related safety topics include:

- As Common Terminology Criteria for Adverse Event grading is not used in real-world settings, surrogate endpoints for assessing severity may need to be developed (e.g. hospitalisations, emergency department visits, treatment discontinuations, use of certain concomitant medications [e.g. steroids]).
- Dealing with duplicate reporting, e.g. patients may have multiple physicians to whom they may report safety events
- Mechanism may be required to assess relatedness (e.g. adjudication)

**Data, methods, and statistics**

- **Standardization of data** to ensure consistency at different sites is desirable, but not always pragmatic. For example, central laboratory testing that may be used for RCTs is generally not used in a real-world setting; providers rely on local laboratories that may have some variability of patient test results and assessments.
  - Differences across countries, sites, platforms, or methods to collect real-world variables provide challenges for the interpretation of the results and the acceptance by regulators.
- **Sample size**: While RPTs may have greater generalisability (external validity) to answer research questions of effectiveness in real-world settings and patient populations compared to the traditional RCTs, heterogeneity of the patient populations may yield lower effect sizes with higher variability, hence often requiring larger sample sizes to detect a significant difference. Studies where large effect sizes are expected could be more feasible in this regard.
- **Missingness:** Missing data either because it was not collected or due to differential frequency of care/loss-to-follow-up among patients is of particular concern for RPTs that rely on the real

patient at the point of care as this can introduce bias to the data. There are multiple statistical methods that can be considered to address missingness (Little et al. 2022 [27]). Selection of a clearly defined estimand is particularly important for RPTs as intercurrent events may be more common and impact not only the missingness of data but also the interpretation of treatment effect (Gedeborg et al. 2019 [28], Gogtay et al. 2021 [29], EMA 2020 [30]). However, these may be challenging and numerous to identify *a priori*.

- **Randomisation** is used to balance known and unknown baseline characteristics to reduce bias and increase confidence in causal effects of the treatment of interest. While propensity score or weighting methods may emulate randomisation to balance measured baseline covariates, conducting a true randomised pragmatic study is ideal to reduce bias from both measured and unmeasured confounders. Patient-level or cluster randomisation may be used. Cluster randomisation (e.g. site-level) could offer some efficiencies and minimize any bias from a provider treating patients in an intervention and control arm (i.e. reduce contamination between arms; Cook at al. 2016 [31]). However, there may be ethical and regulatory questions that arise with alternative randomisation strategies (Anderson et al. 2015 [32]).
- **Blinding:**
  - Blinding patients and/or providers to randomised treatments is a strategy used to mitigate bias and strengthen internal validity for traditional clinical studies. However, in real-world settings using a blinded design reduces the pragmatism of the study (Gamerman et al. 2019 [33], Ford and Norrie 2016 [34]) and may not be possible (e.g. ethical reasons, preferences).
  - In circumstances where an objective primary endpoint can be used some of the potential bias with an unblinded (i.e. open-label) design can be mitigated. However, in an unblinded study the potential for cross-over exists particularly if substantial benefit is demonstrated in the experimental arm compared to the standard of care.

**Operational considerations**

- Pragmatic trials often utilize data generated in the course of routine care and are set in regular clinical practice. Physicians and staff often have limited capacity, training, and infrastructure to conduct clinical research. To avoid additional burden for the health care providers and study participants, it is recommended that **study procedures be simplified** as much as possible. The simplified procedures will reduce interference of the trial conduct with routine clinical practice.
- Where the health system allows, the trial could be organized with a **reduced number of sites** which are responsible to coordinate the study activity, identify and consent potential participants, and manage the data capture process and safety reporting (e.g. DanFlu-1 trial; Johansen et al. 2022 [35]). This will reduce requirements for infrastructure, study-specific and other formalized trainings, and time allocated by physicians to learn the procedures. An agreement with the relevant decision-making bodies may be needed for establishing the adequacy of safety monitoring.
- Pragmatic trials with authorised medicinal products could benefit from **simplified informed consent procedures**. In Europe, it is currently possible for low-interventional trials with cluster randomization that are performed in a single member state of the EU (see Article 30 of Regulation (EU) 536/2014 [36]) to be the subject of simplified consenting procedures. Acceptance of a simplified consenting process across EU members for pragmatic studies, irrespective of classification as low-interventional, would further enhance the real-world character of pragmatic studies, the applicability of the results, and support recruitment.
- Inclusion of **sites reflective of normal clinical practice** will increase the relevance of the trial results by measuring the impact on outcomes in the setting and population where the drug is intended to be regularly used.

- Dispensing trial medicinal products from the trial site defeats the pragmatism of the trials and adds complexity. Where possible, it is recommended that the **delivery of the trial medicinal products** is managed in a manner that is consistent with clinical practice using a co-pay support system and blinded pharmacy personnel where necessary to mimic drug dispensation in regular practice.
- There is a need for a clear understanding and **focus on the most relevant outcomes** in the real-world setting, employing outcomes regularly used in clinical practice, or simple outcomes that do not require adjudication (e.g. overall mortality vs. cardiovascular mortality). Keeping the trial close to regular clinical practice (i.e. minimizing trial-specific requirements) will help prevent/limit medicine non-compliance patterns and avoid poor or incomplete assessment of outcomes that can obscure the effects of the randomised trial and lead to failure in a superiority study or spurious success in a non-inferiority study.
- Different approaches to **data extraction from EHRs** should be considered/developed beyond electronic case report forms. Examples include the RECOVERY trial (Normand 2021 [11]; RECOVERY web page [12]; ClinicalTrials.gov NCT04381936), which used data from national registries, or leveraging efforts such as the American Society of Clinical Oncology's Minimal Common Oncology Data Elements and One Source Project to enable automated flow of structured data from EHRs into external systems. These systems could allow the automatic collection of baseline data and prospectively collect outcomes data for consenting participants without the added burden of sites to complete a study-specific case report form.
- The **study monitoring and safety assessment strategy** should be carefully considered upfront.
  - The concept of risk-based proportionate approaches to monitor clinical trials is already outlined in an annex of the ICH Guideline for Good Clinical Practice E6(R2) [37]. The COVID-19 pandemic offered opportunities to explore more pragmatic onsite and remote monitoring practices (e.g. remote source data review and verification), which could be of relevance to the conduct of RPTs.
  - Trials with approved molecules that have a well-established safety profile may use less stringent monitoring procedures.

**Regulatory considerations**

As outlined above, there is increasing interest from regulators and other stakeholders in transforming the design and conduct of trials in the EU, for example by facilitating the use of novel designs and/or methodology, under the Accelerating Clinical Trials (ACT) EU initiative [3] and in enabling the use of RWE including the use of randomised trials with pragmatic elements (see Section 3 and 4, Appendix 10.3; Gedeborg et al. 2019 [28], Califf et al. 2022 [38]). This section aims to outline regulatory specific considerations in enabling the use of RPTs.

- **Building an EU ecosystem conducive for the conduct of RPT**
  - **Fit-for-purpose, risk proportionate, and quality by design principles** are important and relevant concepts in designing clinical trials including RPT which will protect the patients and their rights and generate reliable and robust data (e.g. ICH E8(R1) Scientific guideline [14 October 2021] EMA/CHMP/ICH/544570/1998 [39] and ICH E6(R2) [37]; Regulation on clinical trials on medicinal products for human use**,** Regulation (EU) No. 536/2014 [36]). There are several ongoing regulatory and policy activities that are relevant to RPT including:
    - The concept paper ICH E6 (R3) Annex 2 dated 30 March 2023 [40] proposes developing considerations for GCP principles for studies with pragmatic elements and studies which use RWD sources in this future GCP annex.

- The draft Data Quality Framework for EU medicines regulation [15] proposes an approach to characterize and assess if the data quality is fit for purpose and can enable regulatory decision-making.

- **Decentralized clinical trials:** This concept became particularly relevant during the COVID-19 pandemic and aims to enable the use of decentralized approaches beyond the traditional clinical site (e.g. delivery of investigational medicine at home). A Recommendation paper on decentralized elements in clinical trials has been published (Version 01, 13 December 2022 [41]). While the two study concepts are different, the proposed recommendations on DCTs, e.g. trial monitoring using remote access to source data, could facilitate the use of RPTs.
- **Regulatory classification of RPTs**: The Clinical Trials Regulation (EU No. 536/2014 [36]) makes reference to **low-interventional clinical trials** and modified requirements for monitoring, the content of the master file, and the traceability of investigational medicinal products. In principle, such modified requirements could facilitate the conduct of pragmatic trials, however, in practice the classification and acceptability of a study as low-interventional differs across Member States thus making the execution of pragmatic trials across EU countries challenging.
- **Inclusion of RWE in prescribing information:** Currently, most of the information in the Summary of Product Characteristics (SPC) is primarily based on preclinical and clinical evidence from traditional clinical trials as well as post-authorisation safety monitoring. Therefore, this information may not optimally reflect the needs of the "real patient" and Inclusion of RWE from pragmatic trials in the product information could provide additional useful insights for prescribers and patients thereby enhancing its utility for users. Clarity on at what constitutes sufficiently robust RWE for inclusion in product information documents such as the SPC and the patient leaflet will help shape optimizes labelling.
- **Develop demonstration projects to help conceptualize regulatory principles/frameworks, and address regulatory challenges:** It will be beneficial for relevant stakeholders, e.g. regulators and drug developers, to learn how to apply the above mentioned regulatory principles and frameworks. EFPIA proposes to design and execute a demonstration project in close partnership with patients, regulators and other stakeholders as a learning platform to explore tangible solutions in the conduct of RPTs (see proposal in Section 7).

**<u>Additional considerations for future assessment</u>**

Additional topics that should be explored in the future, e.g. through some of the proposed actions in **Table 2**, include:

- **Ethical considerations:** Implementing new clinical research methods (which include designs such as randomized clinical effectiveness trials and cluster randomisation) may require a re-examination of existing ethical approaches in providing oversight of these types of studies. EFPIA proposes an evaluation on whether the conduct of RPTs poses additional ethical considerations beyond those of RCTs. Such an evaluation could be part of some of the activities as outlines in **Table 2**.
- **HTA consideration:** While regulators focus on benefit/risk evaluations and corresponding evidence, HTA bodies generally evaluate the broader impact, e.g. in terms of clinical, economic, societal, and ethical aspects, of an intervention or technology. As such, RPTs could be useful for generating relevant evidence for HTAs and payer decisions while acknowledging methodological limitations as outlined in previous sections. Considering that HTA decisions are ultimately made at the Member State level in each Member State, it will be important to initiate a dialogue on the utility of such studies for HTA decisions. Some of the proposed actions outlined in **Table 2** could support those discussions.

- **Generating evidence during the lifecycle of a molecule:** Different approaches can be taken in generating evidence across the lifecycle of a molecule - for example, a RCT followed by a RPT or approaches such as the recently proposed FACTIVE (Flexible Augmented Clinical Trial for Improved eVidencE generation) trial design, which could enable augmentation of confirmatory RCTs with concurrent and close to real-world elements (Dunger-Baldauf et al. 2023 [42]). The proposed dialogue in the activities outlined in **Table 2** might help decipher scenarios of when the different RPTs could be used.

## 7. Summary of key challenges and recommendations for next steps

**Table 2 Recommendations for next steps**

| Topic | Description | Recommendations for next steps |
|---|---|---|
| Increase awareness and alignment across key stakeholders (e.g. patients, healthcare providers, regulators, drug developers) | Increase awareness on RPTs and their value:<br>• How RPTs differ from traditional randomised trials and the anticipated value they may bring for patients and clinical research, e.g. decrease burden for patients, increase external validity of results, accelerating recruitment, reduce clinical development costs | • Leverage this White Paper to increase awareness across key stakeholders |
| Address operational challenges in executing RPTs | Multiple operational challenges were described in Section 6. Examples include:<br>• Provision of the medicinal products at the point of care is often operationally complex<br>• Physicians and staff: limited capacity, training, and infrastructure to conduct clinical research<br>• Need for consistent classification of investigational/non-investigational medicinal product in the EU and which product would need to be supplied (paid for) by the Sponsor | • Perform a more in-depth analysis of some of the operational and regulatory challenges<br>• Drive for regulatory acceptability across the EU of a simplified process to deliver medicinal product to patients/point of care. For example, use local sources of approved medicinal products (if used for investigation or as comparator) to reduce complexity induced through global sourcing and related activities such as traceability<br>• Reduce complexity and support physicians:<br>  • Provide appropriate training to physicians and staff not familiar with the conduct of clinical trials (as sites may extend beyond academic medical centres and into clinical practice)<br>  • Provide support with IT/technologies particularly if the study will incorporate DHTs<br>  • Leverage technology and integrated data networks (instead of individual sites)<br>  • Simplify informed consent process |

**Table 2 Recommendations for next steps (continued)**

| | | |
|---|---|---|
| Increase acceptance and utility of RPTs for regulatory decisions | ✱ Need to increase regulatory confidence on data validity and completeness including acceptability of real-world endpoints<br>✱ Enable fit-for-purpose effectiveness and safety data collection<br>✱ Limit discrepant assessments from regulatory authorities and Ethics Committees across EU | ✱ Propose EMA-workshop to set up and discuss an action plan while considering all other RWE generation activities<br>✱ Identify relevant use cases (demonstration project) and partner with regulators and other stakeholders to address some of the challenges (e.g. in a pre-competitive consortium)<br>✱ Create a pre-competitive consortium involving patient advocacy groups, physicians, drug developers, academia, digital technology and data providers to design a demonstration project and potentially seek qualification advice from the EMA. Such a demonstration project could focus on the resolution of key challenges in order to unlock broader implementation of RPTs for other projects. It will be particularly important to explore which data would be required to accept the use of real-world endpoints. Involve regulators, representatives from Ethics Committees, and HTA/Payers, Inspectors in the Steering Committee<br>✱ Generate guidance on how to include RWE in product information documents<br>✱ Leverage experience from above mentioned activities to generate EMA guidance and/or involvement in international regulatory dialogue to help ensure a harmonized regulatory framework on RPT. |

DHT=digital health technology; EMA=European Medicines Agency; RPT=randomised pragmatic trial; RWE=real-world evidence.

## 8. Summary and conclusions

Currently, the traditional RCT is the gold standard for providing robust evidence to support a benefit/risk evaluation leading to registration of a medicinal product. In the future, we anticipate that the traditional RCT will only provide a proportion of the total evidence for a medicinal product over its lifecycle (Eichler et al. 2021 [1]). For that reason, we will need to learn how to synthesise data from different sources during the lifecycle of the medicinal product (e.g. traditional RCT, RPT, DHT, etc).

Generating RWE via pragmatic trials could be one of multiple tools to generate additional evidence across the lifecycle of a medicinal product for different purposes. Such studies and the use of DHTs offer an opportunity to address the patient's and regulator's needs, i.e. providing evidence applicable to the "real patient" and increasing the external validity of the results. Moving forward, it will be important that we explore together with regulators and other stakeholders appropriate clinical and regulatory settings where pragmatic trials could be acceptable for regulatory decisions.

Despite numerous efforts to enhance the utility of RWD, we need to overcome several challenges in order to enhance the utility of RPTs to generate high-quality RWE for regulatory decisions. For example, uncertainty on the acceptability of key design elements (e.g. acceptability of real-world endpoints, fit-for-purpose data quality, simplified study-related procedures and informed consent) make the design and execution of RPTs for regulatory decision challenging.

We recommend several actions (**Table 2**) to build on the ongoing RWD efforts and momentum, including raising awareness on this type of studies and their potential value, addressing operational challenges, and increasing regulatory acceptance and utility. For this purpose, EFPIA proposes a more in-depth analysis of some of the operational challenges, e.g. through an EMA-sponsored workshop to discuss some of these challenges, as well as the creation of a pre-competitive consortium to work on demonstration projects collaboratively with other stakeholders (e.g. patients, academia, regulators).

In summary, EFPIA considers that well designed, randomised, pragmatic trials, that include fit-for-purpose data quality considerations, would be a useful drug development tool to generate RWE that can inform regulatory decisions.

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## 10. Appendix

### 10.1 Glossary

**Description of different trial types:**

- **Randomised Controlled Trial (RCT):** *''Explanatory clinical trials, which look at the effectiveness of a particular intervention to improve health in a controlled setting''* [A1]
- **Decentralised Trial:** *"Clinical trials with medicinal products have made rapid advances when it comes to digitalisation and decentralisation. By this is meant the* ***use of digital tools*** *(digital consent, electronic consultations, electronic data collection systems, wearables and other medical devices, etc.),* ***which reduce the need for trial participants to attend physical appointments at a hospital unit compared to a traditional clinical trial*** *(Decentralised Clinical Trials, DCT)"* [A2]
- **Point-of-Care Trial:** A framework which provides an operational approach that can be applied to various trial methodologies, e.g. pragmatic studies. [A3]

**Normal clinical practice:** Although intended to differentiate between a clinical trial and a non-interventional study, Q1.9 of the Question and Answers Document - Regulation (EU) 536/2014 – Version 6.4 [A4] describes what is not "**normal clinical practice**". This includes application of one of several therapeutic strategies including:

- Additional or more frequent/increased diagnostic or monitoring procedures or sampling performed solely for the purposes of the clinical study

  OR
- Any procedures not considered clinical practice for the individual patient within the framework of the National Healthcare System of the Member State concerned with the clinical study

**Explanatory trials:** ''*Clinical trials that are performed under ideal conditions with highly selected participants are termed explanatory trials. Explanatory trials are optimized to demonstrate the efficacy of an intervention in an ideal patient population''*. [A5]

**Low-intervention clinical trial** as defined in Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (Chapter 1, definitions [A6]). See also Q1.9 of the Questions and Answers Document – Regulation (EU) 536/2014 – Version 6.4 [A4].

*Low-intervention clinical trial means a clinical trial which fulfils all of the following conditions:*

*1) the investigational medicinal products, excluding placebos, are authorised;*

*2) according to the protocol of the clinical trial,*

   *a) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or*

   *b) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and*

3) *the additional diagnostic or monitoring procedures do not pose more than minimal additional burden or risk to the safety of the subjects compared to normal clinical practice in any Member State concerned*.

## 10.2 Examples of pragmatic case studies for evidence generation

| Study Name | Product | Sponsor | Disease | Study Design |
|---|---|---|---|---|
| Salford Lung[1] | Once-daily inhaler combining FF and VI | IIS | Asthma and COPD | Practical, community-based, randomised, open-label pragmatic study |
| TOPIRA[2] | Tocilizumab vs prednisone | IIS (financially supported by Roche) | Rheumatoid arthritis | Multicenter, open-label, randomised, pragmatic trial |
| VALIDATE-SWEDEHEART[3] | Bivalirudin vs heparin monotherapy | IIS (funded by the Swedish Heart–Lung Foundation and others) | Myocardial infarction | Multicenter, randomised, registry-based, open-label |
| ADAPTABLE[4] | Aspirin | Patient-Centered Outcomes Research Institute (PCORI) | Atherosclerotic Cardiovascular Disease | Pragmatic, open-label, patient-centered, randomised, EHR-enabled |
| RECOVERY[5,6] | Multiple agents | University of Oxford | COVID-19 | Multicenter, pragmatic, platform trial with an adaptive design to evaluate the effects of potential treatments in patients hospitalized with COVID-19 |
| STAR*D[7] | 4 switch options (sertraline, bupropion, venlafaxine, cognitive therapy) and 3 citalopram augment options (bupropion, buspirone, cognitive therapy) | National Institute of Mental Health | Depression | Multisite, prospective, randomised, multistep clinical trial |
| CATIE[8] | Several antipsychotics | National Institute of Mental Health | Schizophrenia | The CATIE schizophrenia trial blends features of efficacy studies and large, simple trials to create a pragmatic trial that will provide extensive information about antipsychotic drug effectiveness over at least 18 months |

COPD=chronic obstructive pulmonary disease; FF=fluticasone furoate (inhaled corticosteroid); IIS-Investigator-initiated study; VI=vilanterol (long-acting beta$_2$-agonist).

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3) N Engl J Med 2017;377:1132-42.
4) JAMA Cardiol 2020;5(5):598-607.
5) N Engl J Med. 2021;384(8):757-758.
6) See https://www.recoverytrial.net/ [cited 2023 Jun 4].
7) Control Clin Trials. 2004;25(1):119-42.
8) Schizophr Bull. 2003;29(1):15-31.

## 10.3 Landscape analysis: international initiatives and guidance

| Initiative and guidance efforts |
|---|
| ✱ ICH M14 Final Concept Paper Establishment of a new ICH guideline on "General principles on plan, design, and analysis of pharmacoepidemiological studies that utilize real-world data for safety assessment of medicines" 23 March 2022 Endorsed by the Management Committee on 5 April 2022. [A7]<br>✱ FDA public workshop "Leveraging Randomized Clinical Trials to Generate Real-World Evidence for Regulatory Purposes", convened by the Duke-Margolis Center for Health Policy, 11-12 July 2019. [A8]<br>✱ Duke Margolis Center for Health Policy, White Paper: Point-of-Care Clinical Trials: Integrating Research and Care Delivery. Published date 11 May 2022. [A9]<br>✱ Clinical Trials Transformation Initiative on Embedding Clinical trials in clinical practice CTTI. [A10]<br>✱ Coalition for Advancing Clinical Trials at the Point of Care. [A11] |
| **Selected international guidance** |
| ✱ MHRA guidance on the use of real-world data in clinical studies to support regulatory decisions. Published 16 December 2021. [A12]<br>✱ Swissmedic position paper on the use of real-world evidence. 1 July 2022. [A13]<br>✱ ICMRA statement on international collaboration to enable real-world evidence (RWE) for regulatory decision-making. July 2022. [A14]<br>✱ Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry. FDA draft guidance, November 2021. [A15]<br>✱ Considerations for the Use of Real-World Data and Real World Evidence to Support Regulatory Decision-Making for Drug and Biological Products - Guidance for Industry. FDA draft guidance, December 2021. [A16]<br>✱ Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision Making for Drug and Biological Products - Guidance for Industry. Draft guidance, September 2021. [A17] |

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