

The Evidence REVEAL Study: Exploring the Use of Real-World Evidence and Complex Clinical Trial Design by the European Pharmaceutical Industry

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The rapid evolution of science and technology allows innovative approaches to generate new types of evidence about the effectiveness of medical product development so as to speed up patients' access to better diagnostics and treatment. Our study explored how two emerging approaches, the use of real-world evidence (RWE) and complex clinical trial (CCT) design, are currently being used by the pharmaceutical industry to support premarketing authorization of medical product development and reviewed the international landscape for regulatory acceptance of such novel approaches. Combining evidence from a literature review, company survey, and interviews with international regulators and experts, we found that 80% of Europe-based pharmaceutical companies have used RWE and 50% have used CCTs, in some capacity. Further, we present case examples of how companies are using these approaches and how international regulators are preparing for such developments. To conclude, we provide a set of recommendations for European industry and regulators to consider so that these novel approaches achieve their full potential within the EU regulatory system.

There has been increased interest in the development and application of novel approaches in drug development, to accelerate patients' access to better diagnostics and treatment, coupled with the desire to contain the ever-growing cost of research and development. The limitations of the current gold standard, randomized controlled trials (RCTs), include issues with the representativeness of the trial population, significant resource and time requirements, ethical considerations within and across trials, and most importantly, the applicability of the results to a real-world environment. New solutions outside the existing paradigms and standards of the drug development process are needed. Real-world evidence (RWE) and complex clinical trials (CCTs) are two of the emerging approaches that have the potential to drastically revolutionize and accelerate drug development processes in the future.

Our study explored how these novel approaches are being used in the premarketing authorization stage of regulatory assessment. To this end, (i) we examined steps taken at the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), and other agencies to promote and support the use of RWE and CCTs in regulatory decision making and (ii) determined how the pharmaceutical industry employ these methods in practice. The paper also provides case examples to demonstrate regulatory acceptance of data generated by these novel approaches and highlight remaining challenges. The combined evidence serves to contribute to building confidence in the community regarding the use of these approaches and to identify opportunities for improving the regulatory policy environment in Europe.

Real world evidence

RWE in this study refers to any evidence about the health status of human subjects that are derived from routinely collected data collected outside the context of RCTs and as such represents a very heterogeneous set of health data captured and stored in a number of ways. Use of RWE presents an opportunity to boost health outcomes for individual patients in an efficient and sustainable manner, including through the use of innovative digital health solutions, e.g., wearables and smart phone apps that capture precise and continuous patient data. Increased use of electronic health records (EHRs) and the emergence of new platforms for data collection and storage such as disease registries enable rapid access to health data of thousands of patients, paving the way for a new generation of high-quality observational,¹ pragmatic,² and hybrid study designs³ also for premarketing authorization stage of regulatory assessment.

Complex clinical trials

Complex clinical trials in this study are broadly defined as trial designs with features that allow responding to multiple clinical questions within a single study. While the exact definition of CCTs varies across regulatory bodies and task forces, their distinction from traditional RCTs is evident through the application of adaptive design and/or the implementation of subprotocols under an integrated master protocol. Typically, CCTs employ at least one innovative element, such as prospective adaptation, novel use of historical controls, multiple expansion cohorts, Bayesian designs and sub/master protocols. The purpose of such novel approaches is to make clinical trials more flexible, efficient, and fast by cutting

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Received August 25, 2020; accepted October 15, 2020. doi:10.1002/cpt.2103

some of the inefficiencies of the current drug development model and tapping into new techniques for multiplying the impact of clinical trials. For example, CCTs have been shown to reach statistical power with fewer subjects and reduce patient burden as treatment arms can be stopped for futility (therapy or dose). They often involve collaboration and sharing of infrastructure, which enables faster screening of new molecules and identification of new (more relevant) clinical end points at reduced costs. CCTs also employ sophisticated modeling and simulation techniques which can improve the definition of operational characteristics and decision targets. Finally, CCTs may, in principle, benefit from streamlined regulatory review and administrative processes, through the regulatory review of the overarching master protocol, accelerating the approval of the associated substudies.

METHODS

The study was conducted in two stages. Stage 1 involved a review of novel data sources and evidence-generation methods put forward by the various European Federation of Pharmaceutical Industries and Associations (EFPIA) working groups and task forces, complemented by rapid evidence reviews and expert workshops for each topic. Following a prioritization exercise, RWE and CCTs were chosen as the topics of focus for the study. In stage 2, between February and May 2019, data were collected for the selected priority areas to cover policies, perceptions, and specific instances of successful and unsuccessful examples across the major regulatory jurisdictions. Three complementary methodological approaches were employed: (i) literature review; (ii) pharmaceutical company survey; and (iii) interviews with international regulators and experts. Literature review covered both peer-reviewed academic literature and gray literature using keyword search terms in articles and documents published since 2012. The survey with pharmaceutical industry for each of the priority area targeted 39 EFPIA member companies that resulted in 32 valid responses. Finally, 21 international experts and stakeholders were interviewed about the regulatory acceptance of the two priority areas, including from the FDA and the EMA.

Key limitations of the study involve: (i) literature search was performed using keywords in the English language; (ii) company survey focused on the view of EFPIA member companies and thus views of other sponsors of medical product development were not included; (iii) self-reporting by companies may include inherent bias; (iv) variations in responding companies' interpretations of what constitutes RWE and CCT does limit the precision to ascribe to the quantitative survey results, despite our best efforts to clarify with sponsors that their examples were aligned with our current research definition; (v) companies were reluctant to reveal the latest case examples and regulatory experience due to confidentiality concerns; (vi) regional comparability (outside of Europe and North America) was hindered by the challenges to arrange interviews with regulatory bodies. It should also be noted that identifying the use of RWE and CCTs in clinical trial registries, published literature, and regulatory documentation is challenging as these are not labeled as such in any standard format. This hampers efforts to learn from the available stock of knowledge and accelerate progress in medical research and development.

Informed consent was obtained from all participants and ethical approval was not required for this study.

RESULTS

International landscape of support for RWE

Until recently, use of RWE was generally limited to the post-marketing authorization context, informing pharmacovigilance and post-authorization safety studies (PASS). More recently, regulators have moved to embrace the potential of

RWE to accelerate clinical research in the early stages of drug development to provide evidence on clinical efficacy and have started to discuss the suitability of using this new type of data with sponsors where RCTs are not feasible.⁴ The chronology of the main milestones in the use of RWE by the FDA and the EMA is shown in **Figure S1**.

The FDA has worked to advance the use of RWE for drug development following the mandate it received in the 21st Century Cures Act (2016)⁵ “to evaluate the potential use of real-world data (RWD) to generate RWE of product effectiveness to help support approval of new indications for drugs.” To guide future activities in this space, the FDA published a Framework for its RWE Program in December 2018⁴ and guidance on the use of RWE for regulatory decision making for medical devices in August 2017.⁶ The guidance characterizes RWD sources and describes cases where RWE can be used to support regulatory decision making, including extended indication for use, postmarket surveillance, and conditional approval.⁷ At the same time, the FDA sponsors several demonstration projects which look at various aspects of generating RWE from RWD.^{8,9–11} These demonstration projects are conducted in cooperation with major research institutes and industry, and look at areas where RWD are “fit-for-use,” e.g., how EHRs can be used to improve the design and conduct of clinical trials and how results obtained from RWE compare with those from RCTs.⁹

Compared with the FDA, the EMA's use of RWE in its evaluations has been on a more “*ad hoc*” basis. This situation is set to change going forward: The EMA has developed its strategy “EMA regulatory science to 2025,” published in March 2020, which stresses the Agency's commitment to “promote use of high-quality RWD in decision making” throughout a product's life cycle.¹² The strategy also commits to harmonizing data standards, defining data quality, and providing regulatory guidance concerning the acceptability of evidence, over and above initiating pilot studies to compare efficacy/effectiveness evidence generated through both RCTs and observational data sources.¹² In addition, the EMA has taken a number of concrete steps to promote and support the use of RWE. For example, the EMA's Patient Registry Initiative, established in 2015, facilitates data harmonization and consistency within different disease areas and across different national registers while also addressing data gaps.¹³ In 2017, the EMA and Heads of Medicines Agencies (HMA) established a joint Big Data Task Force to explore issues such as data sources and formats as well as the feasibility, challenges, and opportunities for using big data in the regulatory process.¹⁴ In addition, the European Union has funded a number of collaborative projects linked to RWE.¹⁵

Efforts to promote and support the use of RWE are also being undertaken to varying degrees in other jurisdictions, including Canada, Japan, and China. Health Canada has launched a series of projects to bring RWE into regulatory decision making, as part of its 2016 Regulatory Review of Drugs and Devices initiative. In October 2018, Health Canada with its partners organized a workshop¹⁶ on defining decision-grade quality RWE¹⁷ across the product life cycle; they also called on industry to submit high-quality RWE. The project “Strengthening the use

of RWE for drugs” aims to improve Health Canada’s ability to assess and monitor the safety, efficacy, and effectiveness of drugs across the drug life cycle by optimizing the use of RWE.¹⁸ A second, complementary project aims to achieve the same for medical devices.¹⁹

In Japan, the use of RWD is currently limited to postmarketing studies; RCTs are preferred over RWD-based studies, where feasible. However, the use of registry data as a historical control for new orphan drug development and for some medical devices has been reported.²⁰ Japan’s Pharmaceuticals and Medical Devices Agency (PMDA) is expected to launch a consultation on the use of patient registry data for marketing authorization approval in the near future.

Similarly in China, systematic use of RWE to support drug development and regulatory decision making is still under development. However, in 2018, the national drug regulatory agencies approved the use of bevacizumab in combination with platinum-based chemotherapies based on supporting evidence from three retrospective RWE studies. Moreover, China’s Centre for Drug Evaluation published in May 2019 a draft document, “Key Considerations in Using Real-World Evidence to Support Drug Development,” for public review.²¹ The guideline aims to provide clarity on the definition of real-world research, outline the use and scope of RWE in drug research and development, explore the basic principles for the evaluation of RWE, and provide scientific and practical guidance for industry to consider when utilizing RWE to support drug development.

In summary, with the FDA and the EMA leading the way in incorporating RWE into regulatory approval processes, other international regulatory bodies are drawing on published cases and guidelines to develop their own RWE frameworks and guidance.

Use of RWE by pharmaceutical companies

The rapid progress in information technology to collect and store large amounts of health data in digital format and the challenge in cases of high unmet medical need to generate data from RCTs contributed to the increased use of RWE for regulatory decision making of first approval of a drug or line extensions/new indications. In the following, we explore the industry’s experience, based on survey responses from 32 pharmaceutical companies on the use and regulatory acceptance of RWE in the premarketing authorization stage.

The survey results showed that the majority of the companies (84%) have used RWD available to them from routine healthcare practice; data sources included EHRs, disease registries, medical claims databases, drug utilization databases, awareness trial and usage (ATU) studies data, and chart abstraction data. In addition, over half of the companies (56%) have also generated their own RWD on at least one occasion. Four companies indicated that they had generated RWD using wearable devices, through activity monitors; and two companies also reported exploring the use of digital end points. Those who had not generated RWD either indicated that they did not need RWD or that they had issues with validation or data protection.

It is important to note that generating RWE from RWD for regulatory purposes requires rigorous protocols with predefined plans for data handling, analysis, and hypotheses so it is not

data-dredging exercise. Our survey showed that 66% of companies had applied data analytics and predictive algorithms to convert RWD to RWE. Both simple descriptive and advanced techniques have been used, including propensity score matching, machine learning, and logistic regression modeling. In some cases, purchased vendor RWD were converted using the Observational Medical Outcomes Partnership (OMOP) common data model to facilitate cohort selection and natural language processing of unstructured data.

Despite the industry’s extensive experience with RWE, the survey results suggest that RWE is not yet used widely to support regulatory approval processes in the premarketing authorization stage. Less than half of the companies had used RWE on at least one occasion to provide evidence for (i) first approvals (47%), (ii) adding a new indication (44%), (iii) extending an authorized indication (44%), and (iv) adding a new patient population (44%). A smaller percentage of respondents (28%) suggested that RWE was used to support an argument aimed at removing a specific contraindication. Other reported examples of RWE use included increased understanding of natural disease history and confirmation of clinical trial findings on efficacy and safety in heterogeneous populations with various comorbidities and co-medications.

The results also suggest companies are using RWE primarily as a complement to other more accepted data types: 47% of companies had made a submission that used RWE as a data complement, while 19% had used RWE to substitute routine data (e.g., by performing virtual trials “at home”).

It is interesting to note that two thirds of the companies (66%) had sought scientific advice from regulators regarding the appropriate use of RWE within their applications, including from the FDA, the EMA, and National Competent Authorities.

Case examples of RWE use in regulatory approval

The survey also gathered 30 case examples of how companies had used RWE for supporting regulatory assessment. In about half of these examples, RWE was obtained from registry data, while in the other half of the cases, RWE was used from EHRs, in some cases, in combination with registry data. While the scope of the study was defined to cover all disease areas, medicinal product types, and geographical areas, 15 case examples were related to submission to the EMA, of which three cases were also linked to FDA regulatory processes.

Those examples that used registry data included product registries set up to meet postmarketing authorization commitments or specific disease registries. These, however, now gain more prominent use to inform efficacy and preauthorization medicine information and contributed to (conditional) marketing authorizations (six cases), label extensions (eight cases), and changes to summaries of product characteristics (two cases). Six cases made exclusive use of RWE (i.e., not in conjunction with RCT data), and these were all linked to label extensions. In cases where RWE was used for marketing authorization, RWE was used for historical control of single-arm phase II or phase III studies. Half of the studies that used registry data targeted oncology and/or pediatric conditions, where the unmet medical need is the highest and where RCT is not feasible, while the remaining cases covered neurology,

rheumatoid arthritis, diabetes, epilepsy in pregnancy, and constipation. Interestingly, in the latter case, the laxative was approved in the United States, based on an independent RWE study, because the drug was already approved outside of the United States.

The examples that used EHRs largely targeted oncology. In one case, both EHRs and registry data were used in the context of an immunomodulator targeting a life-threatening autoimmune disease. Scientific advice was sought, and positive feedback received on the objective end points from routine medical data. Nevertheless, more details were requested by regulators about the data sources, validity of end points, and confounders.

Selected case examples of RWE use in regulatory approval are available in Box 1.

International landscape of support for CCT

Clinical trial methodologies and regulatory guidance documents involving adaptive design started to be published in the mid-1990s, with a number of targeted initiatives established in the 2000s. Key milestones for the FDA and the EMA are listed in **Figure S2**.

The FDA recognized the widening gap between scientific discoveries with the potential to prevent and cure diseases and their delayed and inefficient translation into innovative medical treatments. A national strategy, the Critical Path Initiative was launched in 2004 for transforming development, evaluation, and manufacturing of medical products.²⁸ Acknowledging the emerging importance of clinical trials with adaptive design, the Pharmaceutical Research and Manufacturers of America (PhRMA) formed a Working Group on Adaptive Designs in 2005 that published a number of papers on good adaptive practices and on adaptive dose–response studies.²⁹

The FDA in turn made efforts to encourage the use of adaptive design and issued draft guidance for industry on adaptive design clinical trials for drugs and biologics in 2010, and on adaptive designs for medical device clinical studies in 2015. On a practical level, the FDA funded research to develop trial methodology. This included the Adaptive Designs Accelerating Promising Trials Into Treatments (ADAPT-IT) project, jointly funded by the FDA and the US National Institutes of Health (NIH), exploring the potential of flexible, adaptive trials for neurological emergencies in confirmatory-phase trials.³⁰

In 2016, the FDA Center for Biologics Evaluation and Research published a paper about its experience with use of adaptive design clinical trials for regulatory approval.³¹ The report showed that regulatory submissions using adaptive design approaches had not increased between 2008 and 2013, contrary to expectations on the back of the 2010 guidance on adaptive design clinical trials for drugs and biologics, particularly for confirmatory trials.

The FDA has recently embarked on further modernizing the clinical trial system following the enactment of the 21st Century Cures Act (2016).⁵ The Act contains several provisions concerning clinical trials, including the requirement for the FDA to issue guidance documents to assist the industry in integrating adaptive trial designs and novel statistical models into drug development.³² As such the following new guidance documents were published for industry in 2018:

Box 1 Case examples: Consideration of RWE in regulatory approval

- *Blinatumomab* was approved in December 2014 by the FDA (under the accelerated approval/ breakthrough therapy program) and in November 2015 by the EMA.²² The use of high-quality RWE in a case of strong unmet medical need facilitated accelerated approval with the FDA and a conditional approval with the EMA. The drug was approved for treatment of Philadelphia chromosome negative relapsed or refractory acute lymphoblastic leukemia. The submission for efficacy decision was based on data from a single-arm phase II trial (large effect size) and from a historical comparator arm of patients receiving standard of care extracted from multiple sites in the United States and European Union.²³ Propensity score matched analyses and inverse probability of treatment weighting of the observational data were used to estimate the effect size. For full approval, the EMA requested a larger conventional confirmatory phase III randomized trial. Two years later, the open-label TOWER study confirmed²⁴ the effect size of the earlier submission where RWE was used as historical comparator arm.
- *Prucalopride* was approved in December 2018 by the FDA for chronic idiopathic constipation, after safety concerns related to possible cardiovascular risk were adequately addressed, including via a retrospective observational study in lieu of a cardiovascular outcomes trial.²⁵ As the drug was marketed in Europe since 2009, high-quality patient-level data relevant to its use was available from five population-based automated health care databases (United Kingdom, Sweden, and Germany). Propensity score matched analyses were performed using logistic regression using an independent coordinating center for the study.²⁶ The overall pooled analyses were consistent with the finding of no evidence of threefold risk of major adverse cardiovascular events in patients with chronic constipation using prucalopride as compared with polyethylene glycol. This example shows that the availability of high-quality observational data for the same drug outside the United States provided an important contribution to establish safety of the product.
- *Zostavax* (zoster vaccine live) was originally approved in May 2006 by the EMA for the prevention of zoster (shingles) and postherpetic neuralgia. Zostavax labeling was updated in November 2018 by the EMA to remove a restriction to coadministration with Pneumovax, a vaccine to prevent pneumococcal infection. The initial restriction to concomitant administration of these vaccines was based on a small clinical trial. The label update was based on RWE from a large independent EHR-matched observational cohort study that showed similar long-term effectiveness against zoster in people who received both vaccines at the same time vs. a few months apart.²⁷

- Adaptive Designs for Clinical Trials of Drugs and Biologics³³
- Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics³⁴
- Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics³⁵

Overall, the FDA has expressed strong support for CCTs and is engaging with industry to promote the use of novel trial designs through public meetings with stakeholders (e.g., the “Promoting the Use of Complex Innovative Designs in Clinical Trials” workshop in 2018³⁶). In 2018, it launched the Complex Innovative Trial Designs Pilot Meeting Program, a five-year initiative which aims to facilitate the advancement and use of novel trial designs.³⁷ The program offers participating investigators the opportunity to discuss their approach with regulators and receive guidance on the effectiveness study with the proviso that agreed-upon elements of design and analysis will be publicly shared, including for drugs not yet approved, for learning purposes.

The FDA offers other formal meetings with trial sponsors or applicants,³⁸ including the Type B preinvestigational new drug application meetings, which are often used by industry stakeholders to discuss the use of novel clinical trial approaches. To support the review work necessary for the assessment of complex trial designs and related data analyses, the FDA plans to further develop its staff capacity.

The need to embrace CCTs has also been widely recognized in Europe. In 2007, the EMA published a “Reflection Paper on Methodological Issues in Confirmatory Clinical Trials Planned with an Adaptive Design,”³⁹ which set out the key issues on emerging CCT design in Europe. A major milestone in potentially enabling the use of CCTs was the EU Clinical Trial Regulation (2014),⁴⁰ which advocates for the development of a new clinical trial information system for trial sponsors of investigational medicinal products and regulatory agencies across the European Union.

The EMA’s strategy “EMA regulatory Science to 2025” highlights the need for cross-sector collaboration to drive the adoption of new approaches that use innovative trial designs, novel end points, complex data capture, and statistical analysis and big data approaches.¹²

More recently, in February 2019, the Clinical Trial Facilitation and Coordination Group of the Heads of Medicines Agencies in Europe released a “Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials.”⁴¹ In order to foster cross-sector collaboration in driving the adoption of new approaches, the Clinical Trials Facilitation And Coordination Group (CTFG), chaired by the Danish Medicines Agency, invited industry and academia to discuss the recommendations and their implications for all stakeholders.⁴² The European Commission and EMA also support research collaborations across academia, industry, and regulators that aim to develop novel platforms and validate statistical design methodologies.

To facilitate adoption of CCTs (and other novel approaches), the EMA established an Innovation Task Force in 2001, a multidisciplinary team including scientific, regulatory, and legal competences, which provides a single access point for innovators to engage in early, free, and informal meetings with the regulator.

The EMA also offers scientific advice and protocol assistance (for orphan designations). While these are formal procedures, they are not mandatory and do not provide legally binding advice to industry; nevertheless, such interactions can help to de-risk the adoption of novel trial designs and lead to positive regulatory acceptance.

Health Canada established an Adaptive Clinical Trial Design working group in 2008. It has developed an internal guidance document on adaptive design for assessors; however, a public document for trial sponsors has not been released as yet.

There is little information on activities related to CCTs in other regulatory jurisdictions. Overall, the perception of experts in the field is that other regulatory bodies are moving more slowly and rely on published cases and new guidelines from the FDA and the EMA. While adaptive clinical trial designs are often used in other regulatory jurisdictions, especially in the oncology space, more complex trial designs are rarer, with relevant expertise and experience lacking at many regulatory bodies.

Use of CCTs by pharmaceutical companies

There are a number of potential benefits in innovating beyond the traditional RCT and designing more flexible trials to accelerate medicine development and reduce associated costs. The high failure rate and the increasing drive toward more personalized treatment put pressure on industry to progress faster, while sharing the limited clinical trial capacity and expertise, and coordinate the associated real-time data flows better.

Our survey results from 32 pharmaceutical companies on the use and regulatory acceptance of CCTs suggests that the industry is familiar with some form of CCT design and related evidence. The majority of companies (78%) designed a CCT on at least one occasion. Examples given include adaptive trials, master protocols with umbrella and basket trial designs, and multiple expansion cohorts. Companies used Bayesian methods including response adaptive treatment allocation, logistic regression modeling, and information borrowing; zone sample size re-estimation and other methods were also used.

The use of simulations to design complex trial parameters emerged as an integral component of CCT design: 72% of companies have used simulation to design parameters to determine sample size, assess end points, inform dose selection using Bayesian decision criteria, define study time and method of interim analysis, and optimize group sequential design. These companies sought scientific advice from regulators on the clinical trial design strategy, including from the FDA, the EMA, and the PMDA, mainly concerned with dose selection based on modeling and seamless design.

However, a smaller proportion (66%) of companies had actually conducted CCTs. Reasons for not engaging with CCTs included little expected added value of learning from interim analysis vs. completed phase II trial, operational challenges, requirement to prepare for many scenarios, and greater risk involved. Those that conducted CCTs for regulatory purposes on at least one occasion did so to provide evidence for (i) first approvals (59%), (ii) adding a new indication (44%), (iii) extending an authorized indication (38%), and (iv) adding a new patient population (34%). Company responses indicated that the purpose of CCTs was to reach statistical power with fewer subjects, compare several treatment options

of a disease simultaneously, and to use pediatric extrapolation and interim assessment for stop/go decisions and sample size adjustments.

A smaller percentage of respondents (28%) had conducted CCTs involving novel clinical end points. Examples provided included novel surrogate end points, minimal residual disease primary end points, and digital end points using activity tracker data in the neuroscience field.

Case examples of CCT use in regulatory approval

The survey also gathered 53 case examples of how companies had used CCTs for supporting regulatory assessment. These trials all had adaptive features including Bayesian dose escalation study, expansion cohorts, sample size reassessment, and dynamic borrowing. In terms of disease area, 32 of the 53 examples (60%) were in oncology, rare diseases, and/or pediatric subjects, where unmet medical need is the highest. Other disease areas included immunological, inflammatory, and cardiovascular diseases, as well as diabetes. Of the case examples where phases were reported, 22 trials were in the exploratory phase (I, II, or I/II) and 17 in later phases (phase II/III or III). In early-phase trials, case examples included mechanism-of-action or biomarker-based studies and, in one case, a pooled placebo arm. Cases related to late-stage trials predominantly involved some form of adaptive design element, but very few represented a genuinely complex trial with, e.g., a master protocol design or platform trial.

Selected case examples of CCT use in regulatory approval are available in Box 2.

DISCUSSIONS

Overview of new knowledge on novel approaches

This study explored two emerging approaches, use of RWE and CCTs to support innovative drug development in the regulatory context. It is encouraging that, according to our survey, the majority of pharmaceutical companies had engaged with the use of RWE from major data sources (registries, EHRs, and claims databases). However, less than half of the companies actually used the evidence for regulatory premarketing authorization. Nevertheless, companies are increasingly engaging early in the drug development process with regulators through seeking scientific advice. This is expected to lead to de-risking of subsequent clinical research and the ensuing regulatory submissions. Perhaps most remarkable is the fact that close to one-fifth of the companies had used RWE to substitute more traditional regulatory data. While the use (and regulatory acceptance) of RWE is not mainstream yet, dependent on context, industry as well as regulators recognize the value of good quality RWE, especially when generating evidence through RCT is not a viable option. Case examples demonstrated that a combination of RCT data or single-arm studies and RWE can lead to early (conditional) marketing authorization and facilitate label extensions. As a positive trend, we identified cases beyond oncology and pediatric conditions, showing the potential for RWE to support regulatory approval of drugs in other therapeutic areas (e.g., epilepsy, diabetes, or rheumatoid arthritis). It was not possible to observe systematic differences in regulatory attitudes (e.g., between the

Box 2 Case examples: Consideration of CCT in regulatory approval

Avelumab is an immunotherapy agent and indicated as monotherapy for a variety of cancers.⁴³ Since 2013, the safety and tolerability of the drug is being determined in a phase I, open-label, dose-escalation trial with consecutive parallel group expansion (*Avelumab in Metastatic or Locally Advanced Solid Tumors (JAVELIN Solid Tumor)*).⁴⁴ The trial has evolved beyond its initial design of 7 expansion cohorts to now include 18 cohorts enrolling more than 1,750 patients and covering 17 indications and 12 different tumor types (colorectal cancer, castrate-resistant prostate cancer, adrenocortical carcinoma, breast cancer, gastric/gastro-esophageal junction cancers, head and neck cancer, Merkel cell carcinoma, mesothelioma, melanoma, non-small cell lung cancer, ovarian cancer, renal cell carcinoma, and urothelial cancer). Following a phase II single-arm trial, *Avelumab* received an accelerated approval in 2017 by the FDA and conditional marketing authorization by the EMA for the treatment of a rare form of skin cancer, metastatic Merkel cell carcinoma. Safety data from the phase I study was used to support the approval. In oncology, this is a valuable study design to target multiple indications and has been acceptable to regulators both in the United States and European Union.

Pembrolizumab is an immunotherapy agent and indicated as monotherapy for a variety of cancers. Since December 2015, the antitumor activity and safety of the drug has been investigated in multiple cancer types in a phase II single-arm multicohort basket study (*Study of Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (KEYNOTE-158)*).⁴⁵ Interim results demonstrated⁴⁶ durable efficacy against advanced cervical cancer. On the basis of the results, the FDA granted accelerated approval⁴⁷ of pembrolizumab for patients with recurrent or metastatic cervical cancer in June 2018.

Dulaglutide is indicated in adults with type 2 diabetes mellitus to improve glycemic control as monotherapy or an add-on therapy. The drug's efficacy and safety were assessed in an adaptive, inferentially seamless, phase II/III, parallel arm, randomized, double-blind trial.^{48,49} It was conducted as part of the FDA Critical Path initiative and data were collected from 111 sites in 12 countries between 2008 and 2012. Scientific advice was sought from the EMA and protocol review from the FDA. The trial was considered to involve many novel aspects and the agencies had methodological concerns about data heterogeneity between phase II and III. Ultimately, the seamless study on its own was not considered sufficient for marketing authorization and both agencies required additional phase III studies. The EMA and the FDA approved the product in 2014.⁵⁰

EMA and the FDA) based on the case examples obtained. This is noteworthy as it may indicate that other regulators quickly embrace the FDA's efforts to provide regulatory clarity for the use of RWE in regulatory decision making.

For CCTs, literature provides information on the use of adaptive design clinical trials rather than the more complex master protocol design. For example, the Drug Information Association (DIA) Adaptive Designs Scientific Working Group 2016 survey⁵¹ shows that adaptive designs are increasingly used by industry, with as many as 1,000 such trials designed, ongoing, or completed over the period 2012–2016. Adaptive trials were used for both exploratory and confirmatory phases for early stopping, treatment group adaptations, sample size re-estimation, or changing end points. Another study⁵² looked at adaptive design in post–phase I trials in 2014/15 and identified about 142 such trials; about 10% of these had been used for EMA or FDA product approvals. Finally, a study⁵³ analyzed EMA scientific advice letters that contained a proposed adaptive design element and issued between 2007 and 2012. Scientific advice was sought more often when companies conducted confirmatory trials; three-quarters of the ensuing trial applications were accepted or conditionally accepted.

Given this historic data, it was encouraging to see that close to 80% of pharmaceutical companies surveyed here had designed CCTs to some extent (adaptive design and/or master protocols) and are increasingly using (complex) simulation to design trial parameters and use them in interim analyses. Exploration of mechanism of action or novel clinical end points are still only emerging. Nevertheless, case examples suggested that companies have engaged with regulators (e.g., FDA, EMA, or PMDA) to seek scientific advice on CCTs to a slightly greater extent compared with RWE. About 60% of the companies used CCTs for generating data to support first product approval. Case examples showed both exploratory and later-phase trials, mainly with adaptive design clinical trials. Similar to historic data, 60% of examples were in the oncology and rare diseases space, but encouragingly, other therapeutic areas were also represented among the examples we gathered in our study.

For both novel approaches, initial case studies are becoming available where new evidence is taken all the way through to regulatory approval. These positive examples could be developed into best practices to enhance the knowledge base and raise the confidence level related to these innovative approaches. Early and continuous engagement of trial sponsors and regulatory bodies are essential to exchange specific experiences, gain mutual trust, and explore further learning opportunities together. Indeed, interviewees stressed that only experience and joint engagement can enable novel approaches to go from “underused and less well understood” to mainstream.

Differences between the FDA and the EMA

Direct comparative reviews on marketing authorization decisions among regulatory bodies are rare in the literature. However where available,⁵⁴ it was found that regulatory decisions converged to a high degree among three agencies: Swissmedic, the FDA, and the EMA. They were found to adhere to the same scientific principles (covered in the various International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use scientific guidelines and standards), therefore suggesting that when diverging decisions were made (10–20% of the 255 cases), these were probably due to differences in value judgements on benefits and risks in the specific cultural and legal contexts as well as

public health priorities. While it is unknown if any of the marketing authorization decisions assessed in this study involved either RWE or CCT, it is likely that consistent regulatory decisions regarding novel approaches require extensive communication and alignment across agencies, so that timely and “predictable” decisions are made.

The FDA has made progress in providing clarity about its intention of using RWE and CCT in regulatory decision making. Some of the recent guidance and frameworks issued were important signaling to industry that the FDA is open to innovative data and trial methodologies. The FDA also seems to go beyond general principles of acceptability and provide specific opinions on methods and tools in context. Our interviewees indicated that the FDA is seen as a flexible and pioneering organization that is ready to encourage innovative approaches. An example would be its openness to consider tumor-agnostic indications,⁵⁵ with the EMA closely following suit.⁵⁶ The FDA’s definition of “clinical trial” also allows for master protocols to be deployed in an administratively efficient manner.³⁴ Similarly, knowledge gained since the FDA published the Framework for its RWE Program in 2018 will be instructive to the global regulatory community, innovative pharmaceutical industry, and other stakeholders. Through collaboration and sharing experiential learnings about innovative approaches, modern global medicine development approaches can further align and advance.

The EMA is considered as a front-runner in tracking and adapting its approaches to innovative data and trial methodologies. It, however, currently lags behind other regulators (e.g., the FDA as well as Health Canada) in terms of communicating its regulatory vision, specifically related to guidance concerning the use of RWE¹⁴ and CCTs. This is not to say that there are no significant efforts in Europe to develop and implement these novel approaches, but the EMA’s leadership in providing clarity to sponsors of clinical trials is less visible. The EMA often turns to formulating general principles that it then expects to follow up with sponsors on a case-by-case basis. Since innovative approaches bring along inherent risks compared with traditional methodologies, the EMA prefers to discuss whether or not a novel feature can benefit a particular study.

The EU regulatory framework also hampers current efforts to introduce some complex trial designs, with the HMA’s CTFG stating that “complex trial designs proposing extensive prospective adaptations [...] also challenge the EU regulatory framework in terms of the definition of a clinical trial and data transparency.”⁴¹

The FDA has substantial resources to run dedicated programs, initiate demonstration and pilot projects, organize large public meetings, and upskill staff to be ready to assess innovative approaches as part of regulatory submissions. The FDA’s centralized structure allows for such challenges to be dealt with in a timely and consistent manner.

The difference in the EMA’s approach to some recent innovations may stem from its distinctly different organizational structure and the resources at its disposal. It is a decentralized agency of the European Union and tasked with coordinating scientific evaluation, monitoring, and marketing authorization activities. Many of the scientific committees and working groups involve experts from national competent authorities of EU/EEA (European Economic Area) member states. The recent

publication⁵⁷ of the European medicines agencies draft network strategy to 2025 highlights that resourcing is an important factor in terms of advancing the European regulatory system in general, and regarding innovative clinical trial designs and methodologies as well as real-world data as complement to clinical trials during the preauthorization phase. It is hoped that in the global endeavor of medicines development, the international experience might serve as a direct example of how regulatory acceptance of RWE and CCT might evolve in Europe.

CONCLUDING REMARKS

The study was aimed to inform policy making on new evidentiary sources and their use in preauthorization regulatory decision making. Proposals were developed primarily for industry and regulatory organizations to continue to support the development of innovative approaches for drug development, in particular for RWE and CCTs.

This is a particularly opportune time in Europe when the EMA has developed its new regulatory science strategy to 2025 and the European Medicines Regulatory Network (EMRN) has presented its draft strategy. The EMA should therefore consider developing an RWE framework to enable the use of RWE for pre-marketing authorization regulatory decision making in Europe. Together with industry, the EMA together with the EMRN could lead the development of RWE standards in the European Union and beyond. To translate the concepts into practice and joint learning, the European Commission and the industry in Europe could jointly sponsor demonstration projects to establish when RWE is acceptable for regulatory decision making.

For CCTs, the European Commission will need to provide clarity on how the new EU Clinical Trial Regulation will be compatible with the efficient running of complex trials. The EMA and the CTFG could facilitate better alignment between regulators for acceptance of complex clinical trials across Europe and beyond. Again, for joint learning, the European Commission and the industry in Europe should jointly sponsor demonstration projects for applicability of CCT design.

As highlighted recently,⁵⁸ regulatory acceptance of novel methods of evidence generation will ultimately be the result of collaboration of academia, industry, and health authorities.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

ACKNOWLEDGMENTS

The study team would like to thank the many stakeholders from industry, academia, and regulatory agencies who contributed their knowledge and views to this study, by responding to our survey and participating in interviews. We wish to acknowledge valuable feedback from Maike Rentel on an earlier version of the manuscript.

FUNDING

The Evidence REVEAL study was commissioned by the European Federation of Pharmaceutical Industries and Associations (EFPIA) in November 2018. Technopolis Group designed the methodology, collected and analyzed the data, prepared recommendations, and drafted the report independently from EFPIA.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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