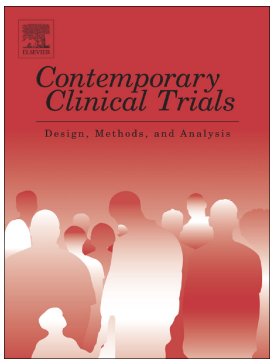

Hybrid clinical trials to generate real-world evidence: design considerations from a sponsor's perspective

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Hybrid clinical trials to generate real-world evidence: design considerations from a sponsor's perspective

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Abstract

Randomized controlled trials have traditionally been the gold standard for evaluating efficacy and safety of medical products and for regulatory decision-making. With the advancement of information technologies, vast amounts of data pertinent to patient health status and health care delivery are becoming available from a variety of real-world sources, including electronic health records, medical claims, patient registries, and patient-generated data. In 2016, the United States Congress passed the 21st Century Cures Act, mandating the U.S. FDA to establish a program to evaluate the potential use of real-world evidence (RWE) for regulatory purposes. In 2018, the FDA published the framework on its RWE program. One particular study type identified in the framework is the ***hybrid design*** – integration of a traditional randomized controlled trial with pragmatic design aspects to collect real-world data on patients. This design preserves the benefit of randomization, provides real-world outcome data while potentially accelerating product development and lowering the cost of data collection and patient follow-up. Here we focus on design considerations for hybrid trials to support regulatory decisions and provide a sponsor's perspective. While applicable to all medical products, we emphasize vaccine development where such hybrid designs are particularly useful given the low incidence rate of some vaccine-preventable clinical outcomes. We propose program strategies on how such hybrid designs may be integrated into a clinical development plan, illustrated by three examples. Major challenges are discussed and recommendations provided. Given the promise of hybrid designs and the challenges in implementation, we encourage proactive discussion with health authorities.

Key Words: real world evidence**,** regulatory decision, hybrid design

1. Introduction

Randomized controlled trials (RCTs) with proactive follow up of study participants for data collection have long been the gold standard for the evaluation of new drug efficacy and safety and for regulatory decision-making [1]. However, it is recognized that the evidence generated by RCTs might not be reflective of the real-world health care settings, nor sufficient for decision making by health care providers, payers, or health policy makers [2]. Moreover, traditional RCTs are increasingly costly to conduct and the cost can be prohibitive in certain disease areas [3]. As a result, post-marketing studies are often conducted to bridge the evidence gap.

With the advancement of information technology (IT) infrastructure, vast amounts of data pertinent to patient health and health care delivery are becoming available from a variety of sources, including electronic health records (EHRs), patient-generated data, medical claims and billing data, and patient registries. While the two latter are not new, advanced IT infrastructure and new analytic tools have made the data more accessible and analyzable. Historically, regulatory agencies have used real-world data (RWD) to monitor the long-term safety of medicines after approval. Recently, there is increasing interest from the pharmaceutical industry and regulators alike to utilize such data for regulatory decision-making on product licensing or expansion of indications. In 2016, the United States Congress passed the 21st Century Cures Act, mandating the U.S. Food and Drug Administration (FDA) to establish a program to evaluate the potential use of real-world evidence (RWE) to support approval of new indications for drugs already approved and to support or satisfy post-approval study requirements.

In 2018, the FDA published its framework on the use of RWE in which *Real-World Data (RWD)* is defined as “data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources”, and *Real-World Evidence (RWE)* as the “clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD” [4]. Among several randomized clinical trial and observational study designs discussed, the hybrid design utilizing RWE for regulatory purposes has the highest potential of being implemented by the pharmaceutical industry and accepted by regulators in the near future.

A hybrid trial is a clinical trial that includes both traditional and pragmatic clinical trial elements [5]. It begins as a traditional clinical trial where participants are randomized to different intervention groups. Some of the data are collected using standardized procedures and case report forms (CRFs) through protocol-defined visits. The remaining data are collected through routine health care visits via sources such as EHRs, medical claims, pharmacy databases, etc. There are several recent examples of such hybrid trials. In the TASTE trial [6], patients with myocardial infarction were randomized and followed

in the Swedish national registry for clinical outcomes. In the ADAPTABLE trial, patients with heart disease were randomized and followed for the outcomes of death, hospitalization for nonfatal myocardial infarction, or stroke using an EHR across a national network of health care providers [7]. Given its high degree of relevance for efficient clinical development of new medical products, in this article we discuss hybrid trial designs primarily for the purpose of informing regulatory decisions. We propose program strategies on how such hybrid designs can be integrated into a clinical development plan and illustrate with three examples. Major challenges are discussed and recommendations provided. While these strategies apply to medical products in general, our emphasis is on a sponsor's view of vaccine development where such designs are particularly useful given the low incidence rate of some vaccine preventable clinical outcomes.

2. Design Considerations of Hybrid Trial

Hybrid trials use prospective randomization to reduce selection bias and minimize the effect of known and unknown confounders, while allowing for flexibility in other aspects of trial execution. An appropriate hybrid design will therefore balance explanatory and pragmatic features, especially if the intent is to provide critical evidence as the basis for regulatory decisions. A comparison of randomized controlled trials, hybrid trials and pragmatic trials is summarized in Table 1.

Table 1. Comparison of randomized controlled trials, pragmatic trials and hybrid trials

	Randomized controlled trials	Hybrid trials	Pragmatic trials
Randomization	Yes	Yes	Generally not but occasionally randomized
Blinding	Generally yes	Yes for outcome assessment (consider for other aspects of trial)	Generally no
Cost per participant	High	Lower	Lowest
Outcome ascertainment	Collected through standardized case report forms (CRFs)	Collected through all sources including CRFs, EHRs, registries or databases. Could consider a nested subset with collection of some outcome data through CRFs	Collected through routine medical sources; electronic health records (EHRs), registries, or other databases; outcome adjudication often required
Sample size	Depends on effect size, incidence of event & variability	Depends on effect size, incidence of event & variability. Usually requires larger sample size than RCT due to more heterogeneous population and higher variability	Depends on effect size, incidence of event & variability. Usually requires larger sample size than RCT due to more heterogeneous population and higher variability
Data quality (internal validity)	Strong, as data accrual is closely monitored. Endpoint is highly specific for treatment intervention. Collection of covariates controlled and standardized across trial sites	Generally lower than RCT but can be improved through outcome adjudication and partial standardized of EHRs across data sources and sites	Quality of data is heterogeneous across RW databases, consistency of capture of patient medical records is variable
Data relevance (external validity)	Limited generalizability beyond characteristics of patients in trial; relevance for routine medical practice is low;	Stronger external generalizability than traditional RCT	Captures routine medical practice & outcomes; generalizability to real-world patients high
Inclusion/Exclusion Criteria	Strict inclusion and exclusion criteria to enroll a more	Minimal inclusion and exclusion criteria so all participants with the disease or outcome of	Minimal inclusion and exclusion criteria so all participants with the disease or outcome of

	homogeneous study population.	interest may be enrolled. May include a subset of participants for which a strict inclusion and exclusion criteria similar to those of RCT will be applied.	interest may be enrolled.

When are hybrid designs most useful?

A clinical trial's design depends on the clinical questions to be answered. Hybrid designs are not a "one-size-fit-all" approach. The choice of a hybrid design needs to be carefully evaluated based on the nature of the disease, the targeted patient population, properties of drug products to be evaluated, the clinical endpoints, and other factors relevant to the trial. In traditional RCTs, clinical endpoints are collected through standardized procedures and protocol-defined visits, while in hybrid trials these endpoints are collected through routine healthcare visits with fewer standardized procedures defined in the protocol. Instead, the assessment of outcomes will depend on the common clinical practice of individual sites and treating physicians as well as their ways of recording them. Thus, endpoints suitable for a hybrid design are those which can be measured objectively with the least amount of diagnostic variability across medical practices such as all-cause mortality, hospitalization for certain specific conditions, or laboratory test measurements. In some cases, endpoints can be validated through the use of a combination of diagnostic terms, laboratory measures and/or medication class use. For a disease condition to be considered as an endpoint, it should be severe enough that patients experiencing the condition will likely seek medical treatment, allowing the events to be captured in the source database. Not meeting this consideration may result in substantial missing data, compromising the hybrid trial's outcome.

Another consideration is the expected treatment effect size. When considering sample size, a smaller effect size or a lower estimate of benefit is expected from hybrid trials compared to a traditional RCT due to the greater heterogeneity of study participants [9]. Thus hybrid trials are more suitable when the expected effect size is high. An underestimation of efficacy can lead to a less favorable cost/benefit profile from a payer perspective. It is possible, however, that such diluted efficacy may simply reflect the effectiveness in a real-world setting.

A vaccine efficacy trial is a good example of the potential use of a hybrid design to bring advantages in feasibility, cost and logistics. Many diseases or infections that are potentially vaccine-preventable have low incidence rates. For example, the incidence rate of congenital infection with Group B Streptococcus (GBS) is only 0.2 to 1.7 per 1,000

births [12, 13, 14]. Among pregnant woman infected with cytomegalovirus (CMV), the transmission rate from mother to fetus is less than 1% [15, 16]. As a result, a trial to demonstrate the efficacy of new vaccine candidate would typically require tens of thousands of participants or a very long follow-up time in order to observe the required number of events. Traditional RCTs would incur huge financial costs for product development [10, 11] or would be logistically unfeasible. Such concerns may deter sponsors from developing a vaccine that might be beneficial to public health. Using a hybrid design to follow up long-term clinical outcomes or infection collected through routine health care visits & RWD improves feasibility, substantially reduces costs, and can also reduce the study duration. Another feature of vaccine trials is that most vaccines require limited administrations over a short period of time. Investigational drug supply is relatively easy to manage, and compliance will typically be higher compared to studies requiring continuous dosing.

In addition to the consideration of event rate for efficacy outcomes, hybrid designs may also facilitate safety data collection, since the trial population is larger and data includes routine health care visits. This is particularly relevant for the development of vaccines for healthy individuals, which necessitate having larger safety databases to assess product safety. Regulators generally require a large safety database for the approval of new vaccine products which will be more feasible with the low per-participant cost of hybrid design.

Data Quality and Relevance

One of the key elements to the success of hybrid designs that seek to collect RWD from routine health care practice is the relevance of the data to the question being addressed in the clinical trial. A key advantage of a hybrid design is that the data collected is representative of real-world health-seeking behavior, medical practice, and outcomes. This is significantly advantageous for the external generalizability of the study outcomes. For example, in studies with endpoints such as asthma exacerbations it would be important to understand whether the full range of outcomes is captured through the ICD-10 coding or EHRs used in the study. The increased use of wearable technology and connected to record biometric parameters such as activity, heart rate, blood pressure and more may offer a unique advantage in hybrid trials as the ability to link wearable data with electronic health records is increasing. Such data allow for the assessment of certain parameters in more continuous manner than what is recorded at specific health care visits.

While clinical outcome data in hybrid designs might be representative of real-world outcomes, internal validity of the data also needs careful consideration. In a traditional RCT, endpoint data collection is strictly monitored and controlled through standardized

collection processes and forms across trial sites. In hybrid designs that rely on routine health care data, ensuring data accrual quality, ensuring data can be extracted from different data sources is an important consideration. It is also important to try and standardize some key data points collection, particularly for EHRs (e.g., laboratory results, diagnosis codes, etc.) across different data sources and organizations where the study is being conducted. While data quality is critical for the clinical outcome, it is important to assess quality of covariate data (BMI, smoking history, previous vaccination status) as well.

Site Selection

Site selection is also critical for the success of hybrid trials as a site's EHR is one of the most important sources of RWD. In July 2018, FDA published the guidance "*Use of Electronic Health Records in Clinical Investigations*" which can be used by sponsors to assess the acceptability of EHR systems [17]. Assessment of EHR system includes whether critical data fields pertaining to the research questions to be answered including drug or vaccine exposure, clinical outcome and important covariates are present, and if not whether these variables can be algorithmically derived using existing data fields. Assessment of an EHR system also includes checking the reliability of the system, e.g., data completeness, internal consistency of data across multiple fields, trends over time, and whether the data of interest is in a structured format that can be readily extracted and compared across systems. Another consideration is the expandability of site's EHR system to add research data modules dedicated to the hybrid trial [18]. Although it may slightly alter the site's routine clinical practice, it should be considered if it could enhance data collection process and reduce missing data. In selecting study sties, medical groups with a large network of hospitals, integrated health maintenance organizations or United States' Veterans Administration (VA) Medical Centers may be preferred to reduce variability in clinical practice and data collection among study sites.

Set-up time is another consideration. For RCTs, trial sites are usually selected and set up relatively quickly, whereas developing a relationship with a health system to collect study endpoint data through EHR systems may take longer. If the system is set-up properly however, it can be re-used for subsequent trials, leading to savings in time and effort in the long run.

Lastly, studies planned in different countries need to be evaluated for differences in clinical practice and the acceptability of these data by stakeholders in countries where the product is to be licensed.

Randomization

The ability to randomize study participants is mandatory for the success of hybrid studies. This can be achieved through individual randomization, cluster randomization or cluster-

crossover randomization [19, 20]. Individual randomization (e.g., stratified randomization or permuted block randomization) is the most commonly used method in RCTs and if properly implemented, will ensure balance in known or unknown confounding factors across treatment groups [21].

In cluster randomized trials, groups or clusters of people rather than individuals are randomly assigned to treatment groups. The units of randomization for such trials are usually medical institutions, hospitals, clinics, pharmacies, schools or geographic regions such as villages. The statistical analysis for cluster randomized trials can be performed at either cluster level or individual level, depending on the clinical questions to be answered. Compared with individual randomized trials, cluster randomization trials offer several appealing features, including administrative convenience, increased feasibility of conducting large scale studies, enhancement of participant compliance, and minimization of treatment group contamination [22]. In vaccine trials, cluster randomization by geographic region provides an additional benefit of potentially measuring the herd effect of vaccination.

However, there are some potential issues and challenges associated with cluster randomized trials. First, if the number of clusters is relatively small then there is the possibility of baseline imbalance between treatment groups by chance alone. The risk of imbalance may be reduced using stratified or pair-matched randomization of clusters, though this may not be feasible when number of clusters is too small. Second, sample size planning is challenging. The sample size required for cluster randomized trial depends not only on the effect size of treatment but also the correlation among individuals in the same cluster, i.e., intra-cluster correlation, which is typically difficult to estimate. Lastly, standard statistical methods for analyzing individual level data could not be applied directly to cluster randomized trial. In cluster randomized trial, the unit of randomization is the cluster instead of individual participant and the existence of intra-cluster correlation renders the standard statistical methods at individual level invalid. Special statistical methodologies for cluster randomized trial should be used to obtain valid statistical inference [22] for which the implementation may be challenging.

Therefore it is preferable to use individual randomization when possible. However, in the case where individual randomization is unfeasible and cluster randomization is used, careful attention must be paid to the study planning and statistical analyses in order to obtain valid results from the trial.

Outcome Adjudication

In hybrid trials, data from multiple sources may provide overlapping or even conflicting information. In some situations, data from several structured or non-structured fields need to be combined to determine a participant’s health status or disease outcome. Different

health care systems may use EHRs with different formats and structures, making it difficult to interpret and compare data across varying sources. Hence it may be necessary to have an independent adjudication committee to review selected data elements and determine the clinical outcome. It is also worthwhile considering the need for outcome validation studies prior to the initiation of the study to address these issues with the independent adjudication committee. Ideally this committee should be independent from the sponsor and personnel directly involved in the conduct of the clinical trial. A charter and detailed operating guidance should be put in place before any data are sent to an adjudication committee for review. Whenever possible, the adjudication committee should be blinded to the intervention to avoid potential assessment biases.

Sample Size

Sample size calculation is critical for the planning of any clinical trial, but especially so for phase 3 trials where substantial resources and financial investment are committed. Sample size usually depends on three factors – effect size, variability and attrition rate. These figures may be obtained from the target product profile, or estimated from earlier trials or from existing literature focusing on trial control populations. Unlike traditional RCTs, where the study population is more homogeneous through consistent procedures and processes used to collect research data, data collected from routine health care visits in hybrid trials may have greater variability leading to smaller effect size. The proportion of missing data may be higher for those collected through routine health care visits for several reasons. Participants may not seek health care if the symptom or disease is not severe enough, may visit a clinic that is not one of the study sites, or may have a change in health coverage such that claim data are not fully captured. Compared with a traditional RCT, a combination of smaller effect size, larger variability and higher attrition rate mean that a hybrid trial will require a larger sample size to attain the desired study power. Nevertheless, the increased cost usually associated with a larger sample size will likely be compensated by substantial savings on the costs of data collection and patient follow up.

Blinding and Bias

An unbiased estimate of treatment effect is essential for the assessment of effectiveness of a new intervention and every effort should be made to ensure an unbiased estimate is obtained. From a study design perspective, the two most effective ways to reduce bias are randomization and blinding. Randomization avoids selection bias and potential imbalance in confounding factors between treatment arms. Considerations on randomization are already discussed in the "*Randomization*" section and it is recommended that individual randomization is the preferred method, while cluster randomization has certain advantages and may be used under specific conditions.

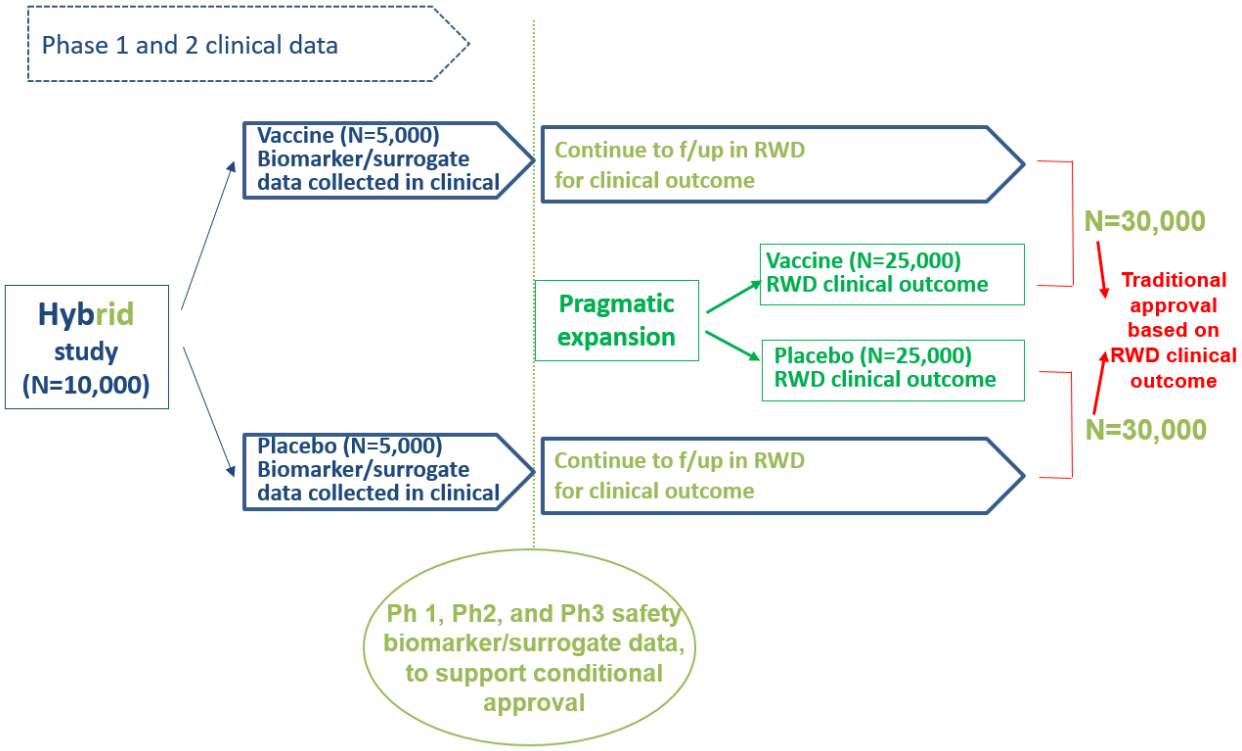
Blinding avoids biases in outcome ascertainment and reporting, and is the common practice in RCTs. However, there is debate as to whether blinding should be used for pragmatic trials. It is argued that blinding health care providers and patients will introduce distortion of both the patient population in the trial and the therapeutic response compared with real life, i.e., the Hawthorne effect. Some suggested that pragmatic trials should avoid blinding with the exception of using blinded assessors of outcomes, whenever possible [23, 24]. However, besides the purpose of evaluating the effectiveness of new treatment in real-world clinical practice, a more important goal of hybrid trials is to generate high quality and sufficient evidence for regulatory decision making. The avoidance of assessment and reporting biases is critical for this particular purpose. Therefore blinding of all personnel involved in the trial including sponsors, health care providers, patients, outcome assesses and data analyst should be maintained throughout the conduct of trial, whenever possible. In the case where blinding is not feasible, at a minimum, the blinding of assessors during outcome assessment should be maintained.

3. Program Strategies for Hybrid Design

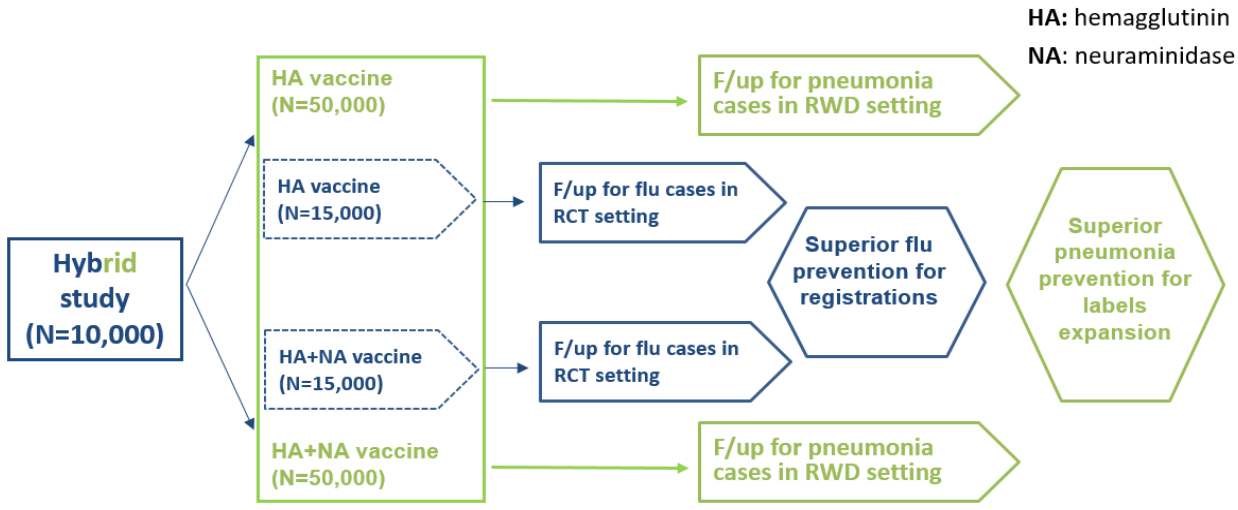
Being able to design a good hybrid trial is unlikely to be sufficient to convince a sponsor to adopt such a disruptive approach. How such an innovative design will augment the sponsor's program strategy is critical in demonstrating its value. For example, is this hybrid study a post-licensure Phase 4 study to support new indications? Or is it a Phase 3 pivotal study to support initial registration? Or will it fit into even earlier phase of clinical development? The following 3 scenarios illustrate where hybrid trials could fit within a new medicinal product evidence generation plan.

Scenario 1

Scenario 2



Scenario 3



Scenario 1 illustrates the case where large hybrid Clinical/RWE study is conducted on a marketed product to update the labels following traditional approval & licensure. This example reflects the case when the drug product is already approved and where the

conduct of additional clinical trials to support new indications would be unfeasible and/or cost prohibitive. This strategy could be used to generate evidence for regulatory decisions such as a new indication to broaden the indicated patient population, update dose regimen or route of administration. It could also be used to demonstrate comparative effectiveness to a current standard of care to facilitate decision making by patients, health care providers, payers or health policy makers. For example, in April 2019, FDA approved the expanded indication of Ibrance (palbociclib) in male patients based on the real-world data from electronic health records (EHRs) and three post-marketing databases: IQVIA insurance database, Flatiron Health breast cancer database and the sponsor's global safety database [25]. This strategy is relatively easy to implement, has precedence for regulatory approval and is likely to become increasingly common in the future.

Scenario 2 illustrates the case where the traditional RCT is expanded to a large, hybrid Clinical/RWE study after conditional approval based on a biomarker or a surrogate endpoint. This strategy applies when the clinical development is still in pre-licensure stage and assumes the regulatory acceptance of an established biomarker or surrogate endpoint to support conditional approval. If conditional approval is granted, then the RCT is expanded to include a much larger study population and to follow up long-term clinical outcome through RWD sources. One variation of the design would be to enroll all participants from the beginning instead of enrolling in two steps. This strategy is riskier as more resources are needed upfront but may be reasonable if the new investigational product is very similar to an already licensed product and the sponsor is confident in the safety profile and likely effectiveness of the investigational product.

Scenario 3 illustrates the case where sponsors are interested in two or more equally important clinical outcomes but some of them are impractical to be collected through traditional RCT due to the rarity of the event, small magnitude of effect size, or where longer term follow up might be required. All participants are enrolled into the hybrid Clinical/RWE study. Clinical outcomes with rare events or smaller magnitude of effect size are followed up and collected through routine health care visits and clinical outcomes with higher event rate or larger magnitude of effect size are collected in a random subset of participants who are actively followed-up like a traditional RCT. After data on all clinical outcomes are collected, sponsors will submit registration application to obtain label approval for all endpoints. In the case where a long gap is expected between availability of different clinical outcomes, sponsors may file submission for one endpoint and subsequently file submission for other endpoints when they become available. For example, in the case of efficacy trial for flu vaccine, it's relatively easier to observe the outcome of flu cases while it will take a very long follow-up time or large sample size to observe required number of pneumonia cases with sufficient statistical power. A potential regulatory pathway is to collect flu cases on a small subset of population to obtain initial

approval with prevention of flu cases on the label. The outcome of pneumonia cases will be collected in the RWD setting on the entire study population to enable label expansion subsequently.

4. Conclusion

The use of RWD/RWE for medical product development is a dynamic area with rapid innovation in the conduct of clinical trials, data collection & data analysis. In this article, we discussed a novel approach, the hybrid design, to conduct clinical trials utilizing RWD. This hybrid clinical trial design has great potential to being utilized within the pharmaceutical industry to generate real-world evidence on investigational and licensed medicines and vaccines. We presented conditions under which such trials might be considered for use, key design considerations and suggest three strategies where such trials might be utilized during clinical development.

We highlight some of the challenges for the implementation of hybrid designs at scale. For example, how do we consolidate data from various sources and transform them into an analysis-ready dataset? How do we handle unstructured data fields captured in EHRs for regulatory decision? What's the impact of each country's privacy rules and the effect on acquisition and use of RWD? How do we conduct global trials if RWD sources are heterogeneous across countries and regions?

We recognize that this paradigm-changing idea will necessitate an integrated global effort across the pharmaceutical industry, health care providers and regulators. In the RWE framework, FDA indicated that the purpose is to evaluate the use of RWE to support additional indications for already approved drugs as well as to satisfy drug post-marketing study requirements. However, a more valuable and nature use of RWE with great potential is to support initial approval for new medical products. With detailed industry guidance on RWE from FDA planned for 2021, sponsors and regulatory authorities need to work together to reach agreement on a feasible pathway for use of such programs in product approval. Experts across different disciplines and expertise will need to come together to develop standardized systems, trial methodologies and operational infrastructure to undertake hybrid trials. There is growing urgency to find novel ways to use real-world data to support regulatory approval of medicines to accelerate availability and reduce the cost of medicines for patients globally. This is a great opportunity for sponsors and other stakeholders to shape the future of medical product development.

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