Harnessing the Benefits of Externally Controlled Clinical Trials (ECTs) to Accelerate Development of Better Medicines

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Introduction

Novel approaches to clinical trial design are crucial to facilitating rapid development of new therapies. In a previous white paper,[1] regulatory agency thinking and decisions around innovative trial designs and the potential for expanding their utility was addressed. Here we discuss the potential to accelerate clinical development by applying an external control arm (ECA) in place of a randomized controlled trial (RCT). ECAs are based either on historical clinical trial or real-world data (RWD) extracted from electronic health records (EHRs), medical insurance records, wearable devices and other sources of patient data.

The digital revolution has considerably enhanced the potential application of real-world evidence (RWE) to support regulatory decision-making. During the COVID-19 pandemic, RWE contributed significantly to patient management and treatment optimization.[2] Nevertheless, ECAs relying on RWD are implemented only in very limited circumstances where application of an internal control is not feasible. Many challenges are faced in the application of ECAs, such as confirming data robustness, matching patient populations, and controlling potential bias. The acceptance of ECAs by regulatory agencies, therefore, requires robust justification involving identifying and addressing all potential biases and confounding factors that might raise concern. Thus, early and detailed discussion with the regulators is crucial.

Artificial intelligence (AI) could play a significant role in analyzing RWE data to identify trends and factors contributing to variability, and so inform on which factors are important to control.[3] Use of AI might allow ECA application to be expanded for other purposes such as optimizing dosage, supporting new routes of administration, and accelerating the development of a broader range of new treatments. Wider adoption of ECAs has the potential to bring treatments to patients faster and streamline drug development, although further advancements in regulatory thinking, methodology and technology are needed before such a goal can be realized.

What is the current regulatory position on use of external controls?

It is important to present a strong justification to the regulators for an externally controlled trial (ECT) to be accepted as a pivotal trial supporting marketing approval. Currently regulators are unlikely to agree to an ECT in circumstances where an internal control would be feasible. Both EMA and FDA strongly recommend seeking early advice when a sponsor intends to utilize an ECT as the primary evidence supporting marketing approval.

US regulations and guidelines

US Regulation 21 CFR 314.126[4] notes that historical controls are usually reserved for special circumstances, such as diseases with high and predictable effect or where the effect of the treatment is self-evident. The FDA draft guidance on "Demonstrating substantial evidence of effectiveness for human drug and biological products"[5] notes that externally controlled studies may be used in some circumstances such as "life-threatening and severely debilitating diseases with an unmet medical need, and for certain rare diseases", but interestingly also "potentially even for more common diseases where the availability of existing treatments make certain design choices infeasible or unethical." The guidance on "Rare diseases: common issues in drug development" gives similar recommendations.[6] The design and analysis of externally controlled trials, including discussion of threats to the validity of trial results from potential bias, is also addressed in detail in the FDA draft guidance on "Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products."[7]

EMA approach

European regulatory bodies have also shown intense interest in exploring the potential value of RWE. On 14th June 2024 the Joint Heads of Medicines Agencies (HMA) / European Medicines Agency (EMA) Big Data Steering Group Workshop on RWE methods held a workshop on "Harnessing Real-World Data for Regulatory Use" to gather perspectives on the draft real-world evidence (RWE) reflection paper,[8] discuss priorities for future regulatory guidance development and collaboration, and engage stakeholders regarding novel RWE methods in regulatory decision-making.

EMA has recently released guidance on using single-arm trials (SATs) as pivotal evidence in drug development.[9] This guidance excludes studies applying external controls but notes that many of the principles for SATs also apply to ECAs. It is emphasized that SATs are accepted as pivotal evidence for safety and/or efficacy only in exceptional circumstances and where justified and refers to Part 4 of Directive 2001/83/EC, which states that: "In general, clinical trials shall be done as 'controlled clinical trials' and if possible, randomized; any other design shall be justified".[10]

In what circumstances are ECAs acceptable as primary evidence for marketing approval?

Only in very few circumstances have externally controlled studies been accepted as primary evidence to support marketing authorization. Mainly, this has been 1) for ultra-rare diseases, or 2) where unmet medical need exists, or 3) where an internal control is not feasible; usually, at least two of these criteria have applied.[11] Figure 1 shows the proportion of products approved in the US and EU where the pivotal data supporting marketing approval relied on real world data and/or external control arms.

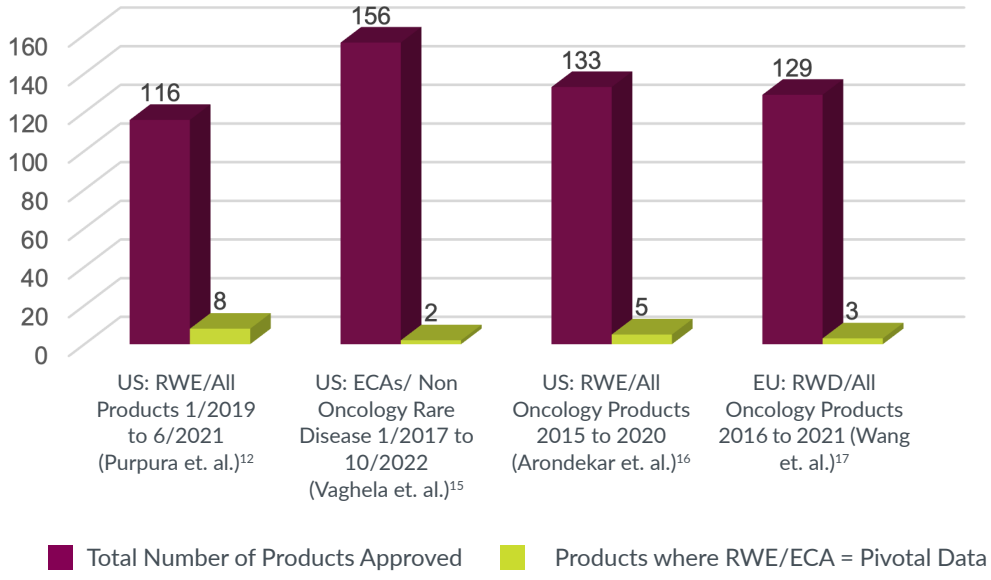

Figure 1: Proportion of products approved in the US and EU where the pivotal data supporting marketing approval relied on real world data and/or external control arms

Precedence in the US

Purpura et al., reported that between January 2019 and June 2021, 8/116 FDA new drug approvals used RWE as reference data to support pivotal studies. Primarily these were for oncology, infectious disease, and neurological indications.[12]

Vaghela et. al. reported that between January 1, 2017 to October 31, 2022, 2/154 products approved for non-oncological rare disease used ECAs to support the primary efficacy analysis.[15] These were pteromalid for treating tuberculosis[13] and thiotepa for Class 3 β-thalassemia.[14]

Arondekar et. al reported that between 2015 and 2020, 5/133 US oncology product approvals relied on RWE for statistical comparison; these were blinatumomab (2018), entrectinib (2019), erdafitinib (2019), selinexor (2019) and tafasitamab (2020).[14] No advisory committee meetings were held, indicating no uncertainty in efficacy or safety. In all cases there were high response rates of >70% where no responses would be expected in the absence of treatment. The extent of FDA's critiques on these studies was broadly inversely correlated with the levels of efficacy achieved.[16]

Precedence in the EU

Wang et. al identified 18/129 oncology marketing approvals between 2016–2021 that employed external controls of which 15 were for new drugs. Of these, in only three cases was RWD derived ECA(s) accepted as pivotal supportive evidence, namely for cemiplimab, axicabtagene ciloleucel, and dinutuximab, all of which showed strong effect when compared to the external controls derived from RWE.[17]

Differences in FDA and EMA thinking

Differences in FDA and EMA thinking relating to ECAs is illustrated by the approval of ciltacabtagene autoleucel for treatment of refractory multiple myeloma. This was approved based on an ECA study, CARTITUDE-1. The ECA was based on data from a well-conducted RWE study. The FDA review team recommended regular approval based on the determination that the applicant had met the statutory standards for "substantial evidence of effectiveness and safety based on a single adequate and well-controlled trial."[18] Based on the same study, EMA granted a conditional marketing authorization (MA) with additional measures required to address the "missing efficacy data" and required that the MA holder submit the results of an ongoing randomized controlled study, CARTITUDE-4.[19]

Application of ECAs outside rare diseases and cancer

The use of external controls is not unique to rare diseases and cancer alone; treatments for more common chronic diseases have been approved based purely on an external control, these include products for treating hepatitis C (edipasvir and soposbuvir) and for partial seizures (lacosamide monotherapy).

Edipasvir and soposbuvir combination was investigated for the treatment of hepatitis C in three ECA studies comparing different treatment schedules but without an internal placebo control arm. In these studies, efficacy in terms of sustained viral response (SVR) rates was near 100% for the investigational arms, compared to a rate of 60% derived from the upper bound of the 95% confidence interval of the highest SVR rate for pegylated interferon and ribavirin from historical controls matching the trial population.[20,21]

The approval of lacosamide as monotherapy in the treatment of partial seizures is another example of where an ECA has been used in circumstances where a prospective randomized control arm was not feasible in a non-rare indication. Placebo or pseudo-placebo (low-dose active) controlled trials are not considered ethical in this indication and, consequently, FDA accepted a monotherapy trial that used a historical-control group based on pooled "low-dose active control" data from historical trials to allow extension of the dosing recommendations to include monotherapy alongside already approved add on therapy.[22, 23] In this case, the ECA was constructed based on a meta-analysis of eight similarly designed trials, incorporating pseudo-placebo control groups. The primary endpoint was percentage of patients who met predefined exit criteria because of lack of efficacy, which was determined as 85.1% for the ECA and 28.9% for the lacosamide treatment arm, thus providing clear evidence for efficacy.

Key considerations in regulatory acceptance of ECA studies

The application of an ECA in pivotal clinical studies supporting regulatory submissions will be subject to intense scrutiny and requires a case-by-case analysis to ensure that the external data are fit for purpose in the specific settings. In this respect, ECAs should be prospectively planned, and prior discussions with the regulatory agencies are essential.[24]

When deciding whether to use an ECA, there should be detailed consideration on addressing potential biases, which may occur even in the most optimal circumstances, such as a changes in treatment paradigm or a shift in endpoint assessment over time, as well as biases arising from prior knowledge of the treatment.

Endpoint selection

To gain regulatory acceptance for an external control trial, it is important to select an endpoint that is both clinically meaningful and associated with a relatively large effect compared to the reference treatments. In addition, trials that are reliant on an ECA, need to apply an objective primary endpoint. There are rare occasions where a subjective endpoint has been accepted because the effect size was so large that it could not be attributed to other sources of variation. Burosumab to treat X-linked hypophosphatemia is such an example. The reduction in total Rickets Severity Scale scored by a radiologist was 50–59% versus 12% for the historical control — and this coupled with the unmet medical need supported pediatric approval.[25]

Natural history of the disease

It is important to understand the natural history of the disease being treated when using real-world evidence as a source of external control data. Applying real-world data to diseases that flare and remit is clearly more challenging. It is also challenging to apply external control arms two time-to-event endpoints due to the difficulty in defining time zero.

Patient selection criteria

The patient population included in the external control arm must be comparable to that in the test arm. Factors such as duration and severity of disease, concomitant disease, prior and concurrent therapies, ethnicity and cultural factors can all impact response rates as can the methodology used for patient assessment. It is interesting to note that in the development of biosimilars, the same reference product has been used in multiple similarly designed studies but results for that reference product can vary within a 20% range or more. Taking adalimumab as an example, from marketing submissions approved between April 2017 and December 2020, results for the primary endpoint, ACR20 response rate at week 24 varied between 64.6% and 82.7% for the same reference product. This hints at the challenges associated with accurately assessing effect based on an external control arm and how population and temporal differences can impact results.

Sources of external control data

The first step in designing an ECA trial is to determine its feasibility in terms of whether adequate external evidence exists, e.g., in the form of historical clinical trials or from RWD. Potential data sources are shown in Figure 2 in order of their robustness.

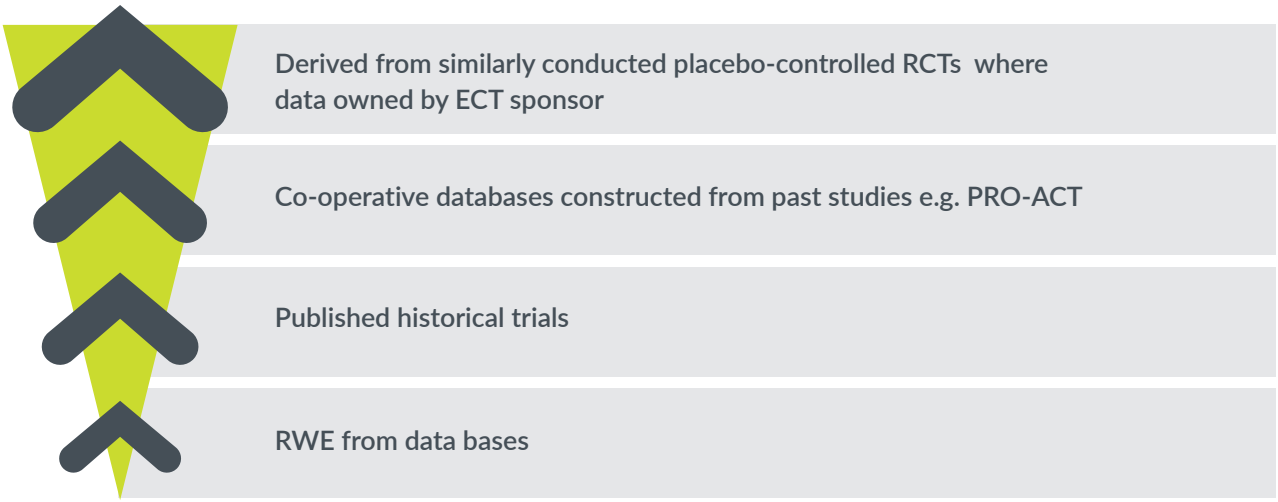

Figure 2: Sources of external control data

ECA derived from similarly conducted placebo-controlled trial

The optimal situation is that the ECA is derived from similarly conducted placebo-controlled trials where the data is regulatory compliant and owned by or accessible to the sponsor. The extension of the indication of ravulizumab to neuromyelitis optical spectrum disorder (NMOSD) represents such an example. In this case, key factors favored the use of an external control: 1) the sponsor owned the ECA data derived from a prior study, 2) the condition was rare, and 3) use of placebo would be unethical in that alternate treatment existed. Furthermore, there was a strong effect size with no patients on ravulizumab (n = 58) having an adjudicated relapse over 84.0 patient-years compared to 20 patients over 46.9 patient-years in the placebo group of the reference trial (PREVENT) from which the ECA was derived. This gave a relapse risk reduction of 98.6% (CI = 89.7%-100.0%).[26]

Co-operative data bases

Creating databases of control arms from past studies represents another robust approach to expedite development of a robust external control arm. This has been done for ALS with PRO-ACT (Pooled Resource Open-access ALS Clinical Trials) which contains 11675 anonymized ALS patient records from the placebo and treatment-arms of 29 Phase II/III clinical trials.[27]

Use of RWD

Justification of the ECA is often more challenging when reliant on RWD. While the same regulatory requirements are relevant to all ECAs, when using RWD there exists greater complexity in addressing requirements as shown in Figure 3.

1	Establishing prior and concomitant therapies used and matching these in the study protocol
2	Confirming the robustness, reliability, and comprehensiveness of the data collection process
3	Adequately addressing whether the external control population is sufficiently similar to the investigational trial population
4	Confirming that the outcome measures of interest are defined and measured appropriately and in line with the proposed external control trial
5	Understanding the potential for bias and addressing biases
6	Dealing with missing data or complete lack of data
7	Accommodating potential impact of geographic, ethnicity and cultural factors.

Figure 3: Points for justification for the use of RWD

Due to the heterogeneity of RWD and potential confounding factors and biases associated with its use, there remains considerable resistance to its application as primary evidence to support marketing approval by regulatory agencies. Vaghela et. al. reported that in rare disease FDA had expressed concerns about the implementation of RWD in 55% of the applications that included RWE. These concerns mainly revolved around aspects, such as 1) differences in baseline characteristics, 2) differences in inclusion criteria, 3) imprecise population matching techniques, 4) insufficient information on key input elements, 5) the presence of potentially subjective elements in defining study endpoints, and 6) the possibility of selection bias and measurement error.[15]

Wang et.al summarized the limitations of external controls cited by the EMA. These primarily related to 1) the Pocock criteria (see Figure 4), 2) participant heterogeneity particularly due to differences in the standard of care, and 3) limited information on baseline characteristics, especially on significant prognostic factors. EU regulators also expressed concern about missing or different assessments of endpoints in the externally derived data. Other limitations included unclear study design and selection bias.[17, 29]

Another challenge concerns defining time zero, the time point set to determine the baseline. In a randomized trial, the start of follow-up for each participant in both the interventional and control arms is clearly specified as the time of randomization. For the ECA, this will not be clearly defined especially when the target trial is a placebo-controlled trial. Defining time zero for the ECA will be needed and requires in-depth understanding of the trial study design.

Handling RWD

If reliant on RWD this should be collected and analyzed in accordance with the principles of good data practice and good clinical practice (GCP).[30] Additionally, regulators need to be provided with documented evidence that the study was not conducted to favor the desired conclusion. What is more, FDA may require patient-level data to allow the use of RWD. As a result, written agreements with database owners may be necessary. If confidentiality issues are a concern, the third-party provider can provide such data directly to FDA either by opening a pre-investigational new drug application (pre-IND) or supplying data via drug master file (DMF).

The use of RWD is associated with several other complexities as discussed above. Sponsors should discuss early with the regulators approaches for transforming the data to approved data standards. A range of approaches may be used, but with adequate documentation, data can be transformed into Study Data Tabulation Model (SDTM) datasets and submitted to the FDA. There are now some ongoing efforts to connect RWD to CDISC standards.[31]

Hybrid design

In circumstances where an ECA might be a step too far, a hybrid design represents an alternative option. Here a concurrent control arm is supplemented by external data.[27] A hybrid approach in which external control data was added to a concurrent randomized control arm (placebo and/or active) has been used for at least three products (velaglucerase alfa, corticotropin, centruroides anti-venom) developed to treat conditions for which there were no available therapies. Two of these were approved for the treatment of rare pediatric conditions. However, even a hybrid approach carries risks. For example, in a recent submission involving hybrid pivotal trials, the FDA statistician called into question the comparability of the external control group, noting that the externally controlled data provided were not helpful and were challenging to interpret. This led to evaluation at a Cell, Tissue, and Gene Therapy Advisory Committee (CTGTAC) meeting convened on May 12, 2023, to discuss the application. Ultimately, the Committee voted 8-6 in favor of accelerated approval of this gene therapy. Nevertheless, even some of the advisors who voted in favor of approval expressed concerns about the strength of the clinical evidence.[28]

The role of AI in expanding acceptance of ECAs

An AI approach gaining traction is the use of digital twins, which comprises a comprehensive forecast of the participant's future health based on data from previous studies. A trial participant's digital twin provides a comprehensive, probabilistic forecast of what their future clinical outcomes may be if they were assigned to the control group. The procedure involves developing a prognostic score for the outcome under the control treatment based on a historical data set that is independent from the study data and then applying the prognostic score as covariate in an ANCOVA model for the actual data analysis of a clinical trial. This methodology has been qualified by the European Medicines Agency (EMA) as providing primary regulatory evidence from Phase II and III clinical trials with continuous outcomes, and FDA has noted that this approach does not deviate from their current guidance.[32]

AI could also play an enhanced role in interrogating RWD for evidence of trends, factors contributing to variability, robustness of endpoints, etc. For example, RWD can be analyzed to determine if there are any trends over time in terms of e.g. response rates, standard of care or relationship between response and baseline characteristics. In this way, it can be possible to identify factors that are important to control and those that are not and integrate this information into the design of the externally controlled trial.

Designing ECAs requires multi-disciplinary expertise

In all trials involving an ECA, techniques to limit bias need to be established.

The validity of an external control depends on how closely it matches that of a randomized controlled trial (RCT). Six criteria for matching have been proposed by Pocock (see Figure 4).[29]

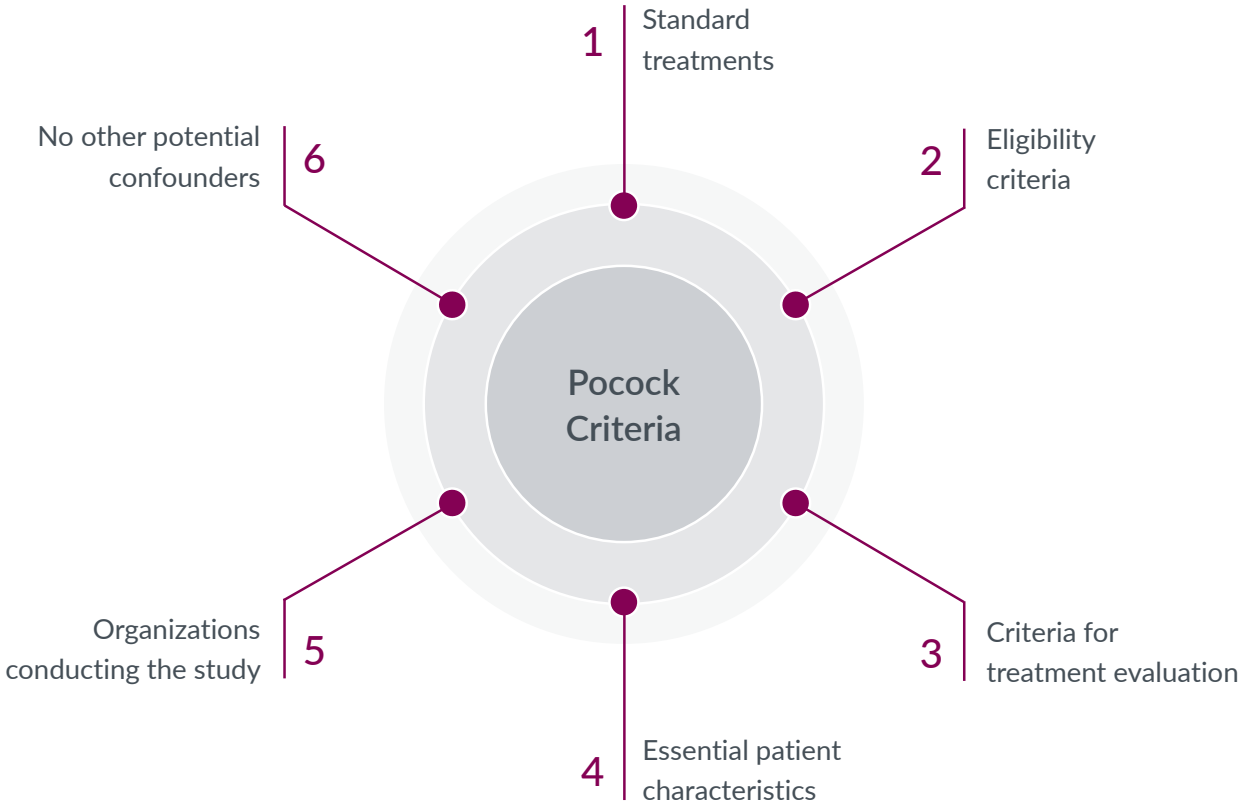

Figure 4: Pocock criteria

Target Trial Framework

The organizing principle in establishing an ECA is based on the Target Trial Framework (TTF), a framework for comparative observational studies of effectiveness, but with a direct application to externally-controlled clinical trials using patients' RWD as the basis of clinical data in the external control.[33, 34, 35] In addition, understanding regulatory stakeholder expectations is also critical for selecting an optimal external control.[7, 36, 37]

The two steps associated with the TTF are illustrated in Figure 5:

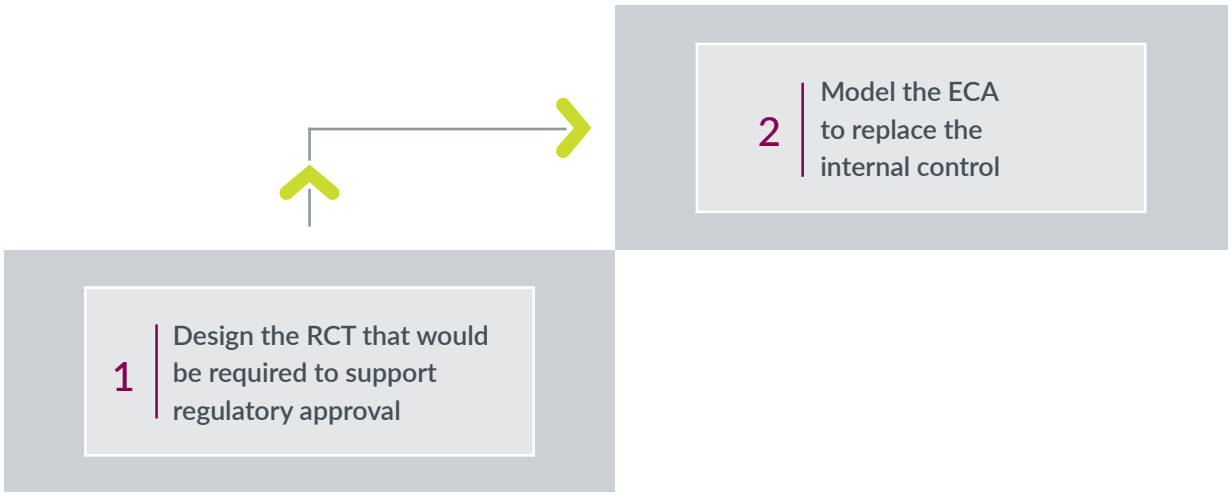

Figure 5: Steps for establishing a Target Task Framework (TTF)

Need for multidisciplinary expertise and statistical teams

Input from experts covering multiple disciplines is crucial to supporting protocol design for an ECT as well as data source identification, addressing potential biases and confounding factors, and ensuring the proposed study's robustness. In terms of statistical analyses, it is recommended that different statistical teams separated by a firewall should be utilized: one team for protocol development and the other for trial data analysis.

Creating for an ECT steering group

We advise creating an ECT steering group and setting up workshops to evaluate the data and options in a structured way and to identify and thoroughly address challenges in design and the potential for bias and confounding elements. The goal would be to establish an agenda and systematically work through the decision-making framework. The steering group would explore, firstly, the feasibility of an ECT and then

develop a study design concept with sufficient detail to engage the regulators for scientific advice and/or approval. The study design concept should be informed by knowledge of regulatory and scientific precedent, including knowledge of specific FDA criticisms and recommendations, guidance and publications.

The steering group should include experts covering the requisite range of disciplines as suggested in Figure 6. Epidemiologists and statisticians can advise and support the adoption of appropriate methods to replicate, as far as possible, the methods that would normally be applied in a comparable randomized controlled clinical trial.

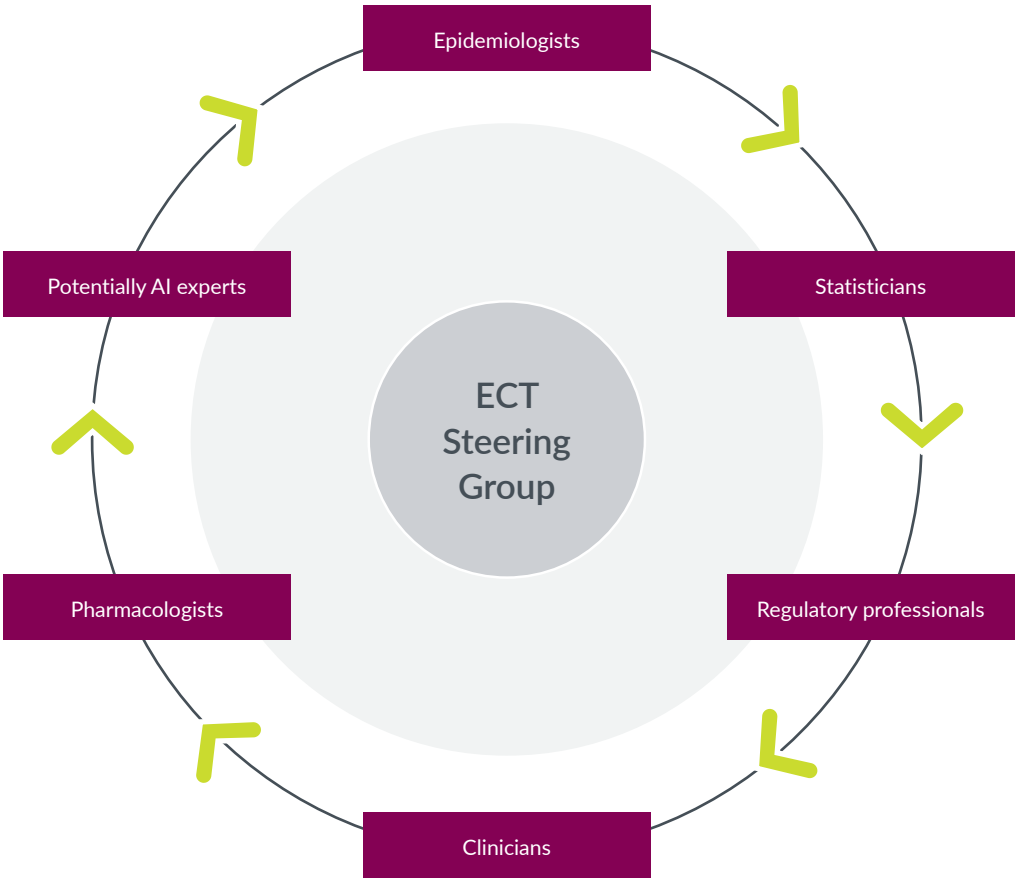

Figure 6: Composition for a proposed ECT Steering Group

Questions that will need to be addressed by the Steering Group are listed in Figure 7 below.

Magnitude of therapeutic effect?	What will be the minimum acceptable magnitude of therapeutic effect of the drug under development in the proposed indication?
Acceptability of RWD?	Would primary evidence based exclusively or partially on RWD be acceptable to regulatory agencies?
Regulatory guidance and precedence?	What regulatory guidance and precedent exist to support and guide an ECT approach?
Adequate external data?	Is there an adequate source of external data? This may extend from RCT data from prior trials to historical or concurrent RWD, with a spectrum of possibilities between these.
Matching regulatory expectations?	How best to replicate the RCT study design that might be expected by regulators and how deviation from the ideal can be justified and mitigated?
Use of AI?	Is their potential to apply AI to mitigate uncertainties?
Addressing lack of randomization?	What are the best methodologies to address the absence of randomization, for example propensity matching?
Optimal approaches?	What are the optimal epidemiological and statistical approaches, including those for mitigating biases?

Figure 7: List of questions needing to be addressed by Steering Group

Statistical approaches to cohort balancing and sensitivity analyses

Cohort balancing

In general, RWD and trial-generated data may differ with respect to several variables relevant to the study outcome, and balancing of these variables is required. There are several different statistical methods available to address cohort balancing; however, use of estimate propensity score (ePS) methods have been preferred, although other statistical cohort balancing methods can be incorporated into the protocol as a form of sensitivity analysis. The ePS summarizes all measured confounders in a single variable and thus can be used in the analysis, as any other confounder, for matching, stratification, weighting or as a covariate in a regression model to adjust for the measured confounding elements. The identification of variables to use in deriving an ePS is, today, typically based on knowledge of the natural history of the disease, which is generally less clear in rare diseases than for common ones. One concern relating to ePS is that unlike random assignment

of treatments, the propensity score may not balance for unidentified covariates (unmeasured and unknown confounders). Such concerns were raised by the FDA relating to external control studies submitted to support approval of the first gene therapy for treating pediatric patients with Duchenne muscular dystrophy (DMD), delandistrogene moxeparvovec, which was approved under the accelerated approval pathway. Whereas the program included placebo-controlled trials, some of the studies were supported by an ECA. FDA expressed major concerns regarding the validity of comparisons to external controls as the treatment effect was expected to be moderate. FDA was concerned this would not easily distinguish treatment response from that in the externally derived placebo arm. Consequently, FDA questioned that propensity scores could not suitably account for the influence of known factors, such as the heterogeneity of the endpoint measurement, and impact of trial related factors on the endpoint or of unknown factors. Nonetheless, the RCT trial was considered adequate to support licensure.[38]

Sensitivity analyses

Sensitivity analyses also play an important role in supporting the robustness of conclusions based on a comparison against an external arm. As an example, the 'tipping point' approach based on the E-value can be applied to assess how robust an association is to potential unmeasured or uncontrolled confounding influences.[39] The "E-value" is related to evidence for causality in observational studies that are potentially subject to confounding. The E-value is defined as the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain away a specific treatment-outcome association, conditional on the measured covariates.

Future ECAs might have wider utilization

ECAs may have wider future application than presented above if a sufficiently robust case were to be presented to and accepted by regulatory agencies such as where the sponsor has accumulated an extensive historical data base replicating the intended trial population. Examples of situations where an ECA could be adopted in these circumstances are provided in Figure 8 below. Such an approach would expand the opportunities for optimizing available treatments and minimize patient exposure to inferior treatment regimens while accelerating development of new treatments.

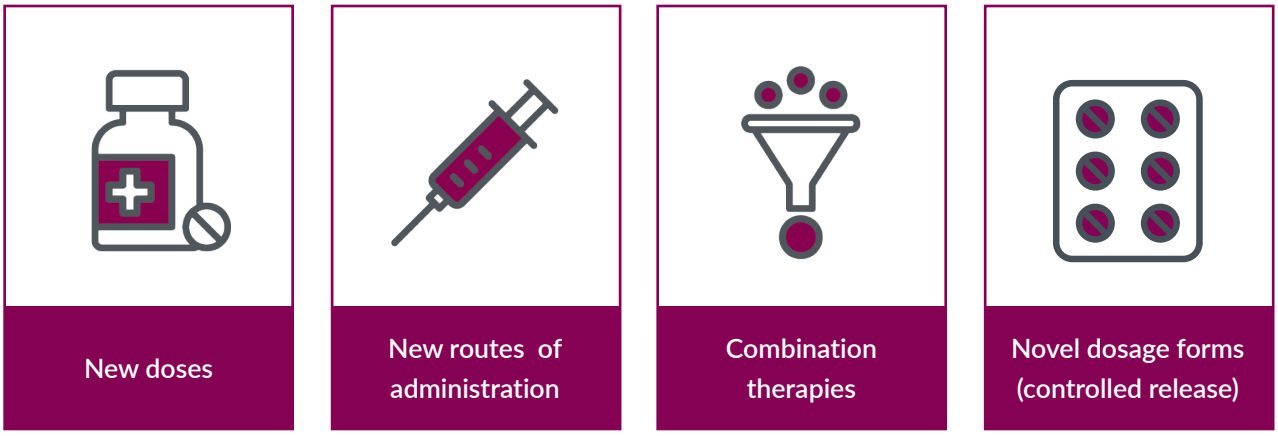

Figure 8: Future applications for ECAs

To shift regulatory thinking towards acceptance of an ECA, a robust and detailed justification would be required. Such a justification would need to address all the factors discussed above - but, in addition, address the importance of rapid approval, such as serving an unmet need or providing enhancement of patient care. In circumstances where patient pools are limited, an ECA could allow for better utilization of the limited patient pool by reducing or eliminating the placebo control group, thus facilitating more rapid parallel development of promising therapies.

Conclusion

ECAs could accelerate the development of new treatments and potentially increase the proportion of trial patients that might benefit from the trial treatment. However, ECAs present challenges and are not readily accepted by regulatory agencies as illustrated by cases discussed in this article. As a result, pivotal trials that utilize ECAs are accepted to support marketing approval only if they can be robustly justified and, currently, where an internal control arm is not feasible. Potentially if the benefit and robustness of using an ECA could be justified, and the challenges and confounding factors addressed, ECAs may have much broader application. The ideal is where the original data sets from historic RCTs are owned by or accessible to the sponsor and where it can be justified that period effects and unblinding will not impact the fidelity of the results. An alternative source of external data is for a stakeholder co-operative effort to develop a robust database such as has been the case with ALS; such databases serve as a rich source for constructing and validating external control arms.[27]

The use of ECAs could be expanded to be applied to support enhancements of existing treatments as well as for novel treatments. Generally, ECAs are best applied where there is well documented natural history of the condition, where effect sizes are large, and where endpoints are objective and not liable to bias. The use of RWD in an ECA is more controversial, but advances in information and digital technology, improving data capture and analysis, should in the future make using RWD more feasible. Another potential approach to the application of an ECA, provided biases arising from the absence of blinding and randomization can be addressed, is to run a non-interventional study while the new treatment is still in the non-clinical phase, to provide a suitable ECA and to inform and accelerate conduct of the interventional trial.[28] Such an approach is likely only to be justifiable in circumstances that lend themselves to acceptance of an ECA.

Wider adoption of ECAs has considerable merit; for faster delivery of treatments for unmet needs, treatment enhancement and streamlining drug development. With advancements in methodology and technology, it is envisaged that ECAs will become more frequently used and accepted in the future.

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