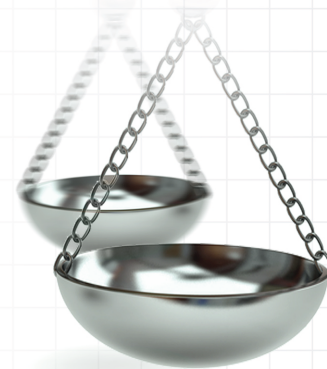




Sieving for gold: external comparator studies to prioritize drugs for late-stage clinical trial

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External comparator (EC) studies can improve identification of compounds with the most promising performance in pre-pivotal single-arm trials (SAT). As SAT output lacks comparative insights, EC studies allow efficient contextualization of compound performance in early phases of drug development. Improving insights from pre-pivotal SATs allows more informed prioritization of compounds and investment choices and enables faster and more substantiated development of the most promising molecules to the benefit of patients. The extensive digitization of healthcare information routinely generated during patient treatment journeys makes EC studies using real-world data an attractive alternative to other approaches (such as systematic literature review and repurposed trial data). Using oncology as an illustration, this paper presents how real-world data EC studies can address some of the fundamental challenges the pharmaceutical sector faces in developing novel therapies, and especially those pertaining to emerging biopharma companies.

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Context

The latest scientific advances have stimulated a surge in the number of new compounds entering clinical trials with over 6000 molecules being investigated globally in 2021 [1]. This proliferation of new investigational products increases the importance for pharmaceutical companies of consciously choosing which therapies to advance for further development and how to efficiently allocate their resources. Emerging biopharma (EBP) companies play a crucial role in this pipeline growth, accounting for about 85% of molecules assessed in pre-pivotal trials (i.e., phases I, II and I–II) [2]. Yet these companies are often financially and operationally limited in comparison to established pharmaceutical companies, and their more focused research and development (R&D) pipelines make them particularly reliant on trial performances of the few (if not unique) molecules they are developing [2]. Moreover, they often focus on rare diseases or small, novel subpopulations, meaning they vie for restricted patient pools and limited funding and resources. In these settings, it becomes essential for EBPs to differentiate and, for pharmaceutical companies more broadly, to identify efficient methods to select the most promising candidates for further development as early as possible.

Table 1. Nonexhaustive sample of articles highlighting the limitations of traditional phase II methodology for predicting phase III success.

Authors	Year	Sample size	Observation	Ref.
Kola and Landis	2004	–	60% of regimens that had ‘promising’ activity in phase II SATs failed to demonstrate superiority in phase III	[12]
Zia <i>et al.</i>	2005	181	81% of phase III studies have lower response rate than in their preceding phase II studies	[16]
Ratain <i>et al.</i>	2005	145	Re-analysis of published data showed the low positive predictive value (27%) of classical phase II trials	[13]
Vickers <i>et al.</i>	2007	134	In phase II studies using prior data to contextualize results, 82% of studies who did not cite the source of their data (46% of studies surveyed) found the agent investigated to be active vs 33% for studies citing the data origins.	[17]
Maitland <i>et al.</i>	2010	363	In 2001–2002, 72% of phase II combination therapy trials were deemed successful but the likelihood that an ensuing trial would demonstrate important effects within 5 years was only 3.8%	[11]

In early drug development stages, especially in oncology indications and uncommon disease with high unmet needs, compounds are often tested in single-arm trials (SATs) to evaluate their safety and initial effectiveness. Positive SAT findings are further confirmed in subsequent head-to-head comparison against standard of care (SoC). While valuable, the lack of an internal control in SATs limits interpretation of their results, impacting not only a true assessment of efficacy but also the design choice for confirmatory trials (e.g., end point selection and threshold definitions). An external comparator (EC) study [3] for an early SAT in settings where randomization is considered not appropriate or feasible can help to mitigate these limitations by contextualizing pre-pivotal trial results against SoC or other emerging therapies and therefore support sponsors’ decisions around a compound’s value and development strategy. This insight may then contribute to increased chances of pivotal trial success, optimize company strategy, and make compounds more attractive to investors.

EC studies represent a fast and economic option, without the operational complexities of a randomized controlled trial (RCT), to provide this additional contextualization and thereby facilitate early compound screening. They can often reproduce the population of interest more accurately and more concurrently than historical trial data or literature review and allow for a direct comparison between SATs and comparator cohorts [4]. Traditionally, they have been used in rare diseases and specific oncology settings where few data exist and they are increasingly accepted in regulatory and market access submissions to complement SATs [5]. Data for EC studies can be generated from various data sources (e.g., registries and historical trial patient-level data), but the approach has benefitted lately from the increasing accumulation of high-quality data in electronic medical records (EMR), enabling the design of EC cohorts resembling the SAT group to the highest degree possible [6].

This article presents the advantages of incorporating EC studies in pre-pivotal trials to inform further clinical development. Notably, this rationale for EC study is different to the intention of replacing a RCT in the further development process of the compound, which seems to have been the perspective of the US FDA draft guidance [7]. By offering early contextualization of trial outcomes, EC studies can enhance insights from pre-pivotal trials, allow for more informed prioritization of compounds and investment choices, and enable faster and more substantiated development of the most promising molecules.

Selecting early-stage compounds based on SAT: is the evidence enough?

Where comparative evidence is not required, the most common trial design to test molecules in early phase oncology is a SAT. This was originally driven by the routine benchmarking of cytotoxic anticancer agents by their ability to cause tumors to shrink [8]. Although tumor shrinkage remains a relevant end point, the focus has shifted to delaying tumor progression and increasing length of survival for molecularly targeted therapies, and even more so for immune-oncological treatments. Due to the course of disease in cancer being highly variable between individuals, the limitations of SATs become obvious [9], with the end points of comparative progression free survival (PFS) and overall survival (OS) (the common key end points of pivotal trials) only addressed in randomized, controlled designs [10]. Instead, they tend to focus on overall response rate for the earliest trials. Large reviews have shown that positive phase II trial results based on SAT seldom correlate with positive phase III outcomes (Table 1). Probably the most complete insights were from Maitland’s analysis of all 363 phase II oncology therapy trials published in

2001–2002, revealing that although 72% of them were deemed successful, less than 5% would go on to demonstrate important effects in ensuing trials (completed within the subsequent 5 years) [11]. Similar results have been observed by Kola and Landis [12] and Ratain [13] who have found that standard, (i.e., nonrandomized) phase II trials have poor predictive value for phase III outcome. Despite these conclusions published more than a decade ago, about two thirds of phase II trials in oncology still have a nonrandomized design [14]. Moreover, a recent systematic review of 111 phase III trials published in 2023 found that the observed hazard ratio was weaker than the assumed value in 57% of cases, suggesting that many trials are underpowered due to overly optimistic assumptions anchored in small phase II cohorts that can overestimate true treatment effect if not adjusted appropriately [15]. An EC study would help mitigate this by anchoring effect size assumptions to real-world or historical data, offering a more realistic benchmark.

The shortcomings of methodological approaches to contextualizing SAT results

Given the limitations of traditional, nonrandomized methods for assessing pre-pivotal trial results [8], sponsors compensate for the lack of a direct control population using a variety of options including expert opinion, literature-based comparison [18], predictive modeling of repurposed trial data [19] and EC analysis [4]. However, each of these approaches have drawbacks. Interpretation of early-phase clinical trials tends to rely on expert opinion only, which can be nongeneralization and limited by incomplete evidence. Literature-based comparison and predictive modeling rely on external study data from a comparative population, which is not always available, and if so, end point definitions, measurements methods and timings may be substantially different in available comparators [20].

For published trial data, matching-adjusted indirect comparison (MAIC) is a statistical approach allowing indirect comparison between SAT results. MAIC requires weighting SAT patient-level data such that baseline characteristics are close to the aggregated data reported in the historical trial. However, MAICs do not address different eligibility criteria, resulting in likely bias. It is also not using all individual-patient level data of both data sources because of unavailability, which would allow for best bias control. Furthermore, it is inefficient where there is poor covariate overlap or reduced sample size after weighting [21]. Finally, interpretation of SAT results using historical data assumes nonsignificant change in contemporary treatment approaches and outcomes, whereas improvements in SoC over time, earlier detection rates and differences in prognostic factors are inevitable for most indications.

Predictive statistical modeling is a more recent approach, estimating from measured variables in SAT patients their outcomes under conditions of no treatment or current SoC [19,20]. Models are built from pooled samples of untreated individuals at the outset of a SAT to predict relevant end points (had these patients been in an internal control group). These outcomes are compared with the eventual SAT results using standard methodologies such as cross-validation [22]. As more data accumulate, prediction equations are refined, and the effect size estimates are upgraded. This approach has been used to predict and compare outcomes of PFS, 1-year survival and OS but suffers from similar biases to MAIC [19]. A large patient pool is generally required to build a sufficiently accurate prediction model and this may be difficult for rare diseases or subgroups.

In contrast to these approaches, EC studies can offer a more accurate reproduction of a population of interest than aggregated published data only [4]

How EC studies could address some of the current challenges in early drug development

The low correlation between phase II success and subsequent phase III positive outcomes has prompted investigators to call for more stringent methods to select which compounds warrant advancing to a pivotal trial [23]. Although it cannot be guaranteed that positive results from an EC study in pre-pivotal stages will translate to success in later trials [24], an EC-backed SAT can provide the first indications of randomized trial results by emulating RCT in a cost-effective fashion. This offers additional valuable information to guide decision-making as outlined in the following scenarios (Table 2).

Better contextualization of SAT results

With robust methodologies and high-quality customizable data, an EC study generally allows the efficacy of a compound to be better contextualized in a population that closely resembles that of the SAT, than where insights are only obtained from published literature. The ability to include EC studies in a statistically robust study design also enables a more objective evaluation of the efficacy (and potentially also the safety profile) of the compound compared with decisions based on individual's experience or less aligned populations from the literature [25,26].

Table 2. How external comparator studies can address current limitations related to pre-pivotal single-arm trials.	
Current problems in early clinical drug development	How an EC study could address them
Low correlation between pre-pivotal and pivotal trial success	An EC study can offer glimpses of potential future head-to-head comparisons which would allow to select most promising compounds, but also tailoring the RCT design to increase success
Companies struggle to select the compounds for pivotal trials given the high volume of compounds in clinical development	Contextualization of early-phase trial results against SoC and levelling of evidence allow to evaluate candidates more precisely, identify the most promising ones for further development and inform future trials
Contextualization of SAT data is only possible via imperfect methods such as indirect comparison with historical data and aggregated data only, or just relying on decision-makers' experience	EC population aligns more closely to the SAT population and statistical adjustments based on individual patient-level data allow for more accurate decision-making
EBP need to attract investors to continue drug development amidst heavy competition	Putting early results in perspective of actual treatment standards, adds confidence in a compound's potential and can differentiate it against competitors in the absence of a head-to-head trial
Companies must convince investigators to participate in further trials	Increasing transparency and documentation of potential benefits to patients can entice investigator to choose a trial
Limited pool of patients to conduct trials	Optimization of the available patient pool without sacrificing statistical power
Mixed results in early phase trials	Inform alternative future trial designs for the compound (e.g., new specific population, different end points or active comparator)
Quickly evolving SoC can make prior results outdated	An EC study provides a fast and agile means for incorporating (close-to) contemporary patients to benchmark results against the latest SoC and inform clinical development
EBP: Emerging biopharma; EC: External comparator; RCT: Randomized controlled trial; SoC: Standard of care.	

De-risking selection of assets for further internal development

Effective portfolio prioritization becomes critical for pharmaceutical companies with extended R&D pipelines, but the exercise is rendered more complex by the unprecedented number of compounds investigated and higher thresholds for efficacy. As limited data are available in early stage, there is significant risk that apparent efficacy of a compound will not translate to comparative efficacy in larger, later phase-controlled studies or that increasing efficacy of SoC meantime reduces the significance of early results. By comparing early efficacy SAT data against SoC or concurrent therapies, EC studies can provide a robust alternative to complement existing approaches. Earlier comparative insights, even in the absence of prospectively controlled studies, can help identify compounds with the best potential for future commercial success if developed, whereas conversely, decisions to drop or reorient development can be made earlier for compounds that do not present a clear benefit.

Attracting investments

Companies with narrower pipelines such as EBP are often dependent on external investors to continue their research program, so it becomes crucial to convince investors that early positive results can translate well into later stage trials, and stand out from a crowded field of similar ventures. An EC study can achieve those two objectives by mimicking a small-scale RCT, thereby delivering a competitive advantage over compounds without contextualized early phase results. This advantage is another application of the de-risking of future performance described above, but with improved confidence for investors being the goal.

Convincing investigators

Other stakeholders for whom de-risking future performance becomes important are research and treating clinicians. Teams must often prioritize involvement in a large number of pivotal trials while having limited resources and staff available to participate. In recruiting study participants, they must often make recommendations to patients with limited information about comparative benefits of investigational therapies against established ones. The increasing transparency on potential advantages and side effects of an investigational compound to patients coming from an early EC study could increase investigators' enthusiasm to participate in larger-scale trials. Compared with a competing RCT with no prior contextualization, investigators might prioritize a pivotal trial backed by an earlier EC study, thereby increasing patient enrolment.

Optimizing patient pool

SAT have been commonly adopted for rare diseases when targeted patients are too few to create a well-powered trial with a comparator cohort or where the decision to withhold treatment for the purposes of a controlled analysis is not ethical. In this instance, an EC study enables the optimization of the SAT analysis (especially in terms of statistical power) by maximizing the pool of comparator patients from multiple sources. It would also mitigate ethical concerns for contemporary high unmet needs by enabling a retrospective comparator population rather than depriving current patients from a potentially beneficial compound [27].

Adapting to quickly evolving SoC

The rapid pace of clinical innovation means guidelines are frequently updated to reflect higher SoC [28] and the level of efficacy new compounds must demonstrate keeps increasing over time. A striking example is the introduction of chimeric antigen receptor-T (CAR-T) and other cell and gene therapy (CAGT) therapies for which sponsors are now required to supplement their RCT with additional evidence to capture the latest treatment landscape. Should it happen during pre-pivotal trial, the SoC shift further raises the stakes of the decision to move a compound to pivotal trial. An EC study provides a fast and agile means for comparing early SAT results against a new SoC and help drug developers to make a more substantiated decision. A fast-turnaround EC study can be even more significant in the scenario where pre-pivotal trials are RCT but a change of SoC has made the comparator cohort of the trial outdated [29]. Using EC studies allow researchers to still exploit precious pre-pivotal intervention data but ensure the analysis remains as current as possible.

EC cohorts are an increasingly accepted & accessible approach

Resorting to EC studies in early-stage clinical development would be the prolongation of the current momentum that saw EC studies becoming a well-established strategy for late phase evidence generation. Methodologies such as the target trial framework successfully emulate internal control arms across multiple tumor types and end points [30,31] and have also replaced RCT control arms *a posteriori*, yielding similar results [32]. Under this framework, a hypothetical target RCT that would answer the research question is designed, before real-world data (RWD) are used to emulate this trial, aiming for conditional exchangeability of patients [20].

The growth in healthcare data digitization has facilitated the design of retrospective cohorts resembling those of SAT, which are rapidly supplanting other data sources for EC studies. As precision medicine and next generation therapies targeting more narrowly defined patient segments emerge, identifying suitable existing control trial data for comparison becomes challenging, even when RCTs' end points and internal control arms are compatible with a SAT. As a result, HTA submissions based on SAT and supported by a RWD EC study increased by 22% between 2015 and 2019 while the use of historical trial EC studies decreased by 14% [33]. Moreover, acceptance rates for RWD EC studies increased by 20%, compared with 10% and 15% decreases, respectively, for submissions using historical trial EC studies and SAT alone [33]. A recent analysis across 33 countries also showed that the proportion of HTA submissions incorporating RWD rose from 6 to 39% between 2011 and 2021, and RWD EC studies had a positive impact on HTA recommendation in a subset of 20 HTA oncology dossiers [5].

The inclusion of EC studies in regulatory submissions has also rapidly increased in recent years with both FDA and EMA publishing new guidance on externally controlled trials and use of SAT [7,34]. EMA submissions for cancer drugs with EC studies between 2016 and 2021 had a 63% acceptance rate, and 17% of all EMA-approved drugs used EC studies as part of their evidence package [35]. In the US, the use of EC studies to provide therapeutic context in new drug applications and biologics license submissions rose from 49 to 85% between 2019 and 2021 [36].

Strategic advantages of EC study use in early clinical development

Given the increasing recognition from authorities and large spectrum of needs they can address and highlighted previously, EC studies can have different purposes for both internal and external strategy. Key arguments are summarized in Table 3.

Company strategy

Drug clinical development has always been a lengthy and expensive process with trial cost doubling from one stage to the other prompting pharmaceutical companies to carefully select which compounds should be further investigated [37]. A phase III trial in oncology costs on average \$48 million [38], which is more than all pre-pivotal trials combined, and the decision to launch a pivotal trial must hence be weighed against that of advancing

Table 3. Summary of benefits provided by contextualization of early-stage trial results by an external comparator study.	
Category	Advantages brought by external comparator studies
Company strategy	Support identification of most promising compounds Inform pipeline prioritization and strategy Better understanding of a compound value proposition Increase potential for differentiation Inform further trial eligibility criteria and end points to improve success rate
External engagement	Support discussions with current/potential investors Contextualize trial performance for analyst reports Encourage investigators/healthcare providers and patients to participate to subsequent trials

a new substance through all pre-pivotal stages. The increase in new investigational products and requirements for therapeutic efficacy driven by pharmacological innovation makes this decision process even more complex: companies must select from a wider pool of investigational products and will need to demonstrate ever-higher clinical efficacy, often in a fast-moving treatment landscape.

We think an EC study can play a significant part in that decision in complement to existing processes. This could be the case in three specific scenarios. First, if the company is only considering one compound to advance to the next development stage (as can be the case for EBP sponsors with a focused portfolio), putting early SAT results in perspective against RWD will enable to gauge the potential improvement the treatment could bring over SoC before a formal efficacy assessment in later stage trials. The second use case would be when a company is considering two candidates for the same indication, as a common EC study for both compounds would then go further than benchmarking each compound against SoC: it would also allow to determine which one would have the highest impact on patients. Finally, large pharmaceutical companies usually have pipelines with several compounds and must make decisions across different therapeutic portfolios. When considering which candidate to continue developing, the early phase benchmarking would bring valuable information about each compound scientific merit, which in addition to other economic considerations (e.g., addressable market, potential pricing points, and odds of being reimbursed), will empower decision-makers to make a well-informed choice.

An EC study might not prevent subsequent trial failure and should not replace formal comparison using RCT design in later stages, but in the absence of comparative data, it presents a cost-effective strategy to better equip pharma decision makers for clinical development: for a fraction of the cost of a pre-pivotal trial, they will be able to hint at a compound potential against selected SoC or key competitor treatments. If results are negative, development should be halted and resources redistributed elsewhere; if they are positive, they provide an additional argument in favor of continuing development.

While the EC study framework has traditionally been associated with SATs, its utility extends beyond this context. For instance, under the new requirements of Project Optimus, many early-phase oncology trials have adopted randomized designs to evaluate different doses of the same investigational product. Although these are not SATs *per se* and ECAs are not suitable substitutes for internal controls in dose selection, they may still offer value in contextualizing early signals such as tolerability or preliminary activity against an established SoC. This is especially relevant once a dose is selected, or when internal data is limited and competitive positioning becomes important. While ECAs cannot guide dose optimisation, their principles remain applicable, offering a cost-effective way to generate comparative insights that support go/no-go decisions in later stages of clinical development. The initial comparison from the EC study can also help to refine the compound value proposition should they provide mixed or negative results. An in-depth analysis of these results can for example help to reorientate the compound toward new specific populations, consider alternative end points or select a different comparator cohort, e.g., by defining an active comparator. The compound could then be tested in light of this information in a new pre-pivotal trial. Generating these insights from SAT data only would be less robust while their knowledge offers a new chance for the compound to show its potential considering new dimensions that are more aligned to its value proposition. By informing key aspects of the compound profile, an EC study can help to reposition the investigational product and improve its chances of trial success while offering the possibility to differentiate it against established ones. A more defined compound with higher chances of success makes it more appealing not only for further development, but also to investors.

Engagement & communication with stakeholders

The value of an EC is not only limited to internal decisions about product positioning and company strategy but can also contribute to communication with external stakeholders. EBP must convince analysts and investors to choose their program for funding over similar ventures. Investors need robust evidence of a treatment's effectiveness and its benefit potential before they agree to inject funds in a company [39], yet they face the same problems as pharmaceutical companies when deciding which assets to advance for further clinical development: the information generated from pre-pivotal trials does not always allow for a well-informed contextualization of the product efficacy in the current treatment landscape. In the absence of comparative results, investors' decision can hinge upon a combination of factors such as the compound's early efficacy and safety signals, patients' unmet needs, the current treatment options and the future competition, the compound's addressable market or even the hype underpinning its technology. In these scenarios, speculation plays a significant role in their decisions and real-world comparative data could help to establish more objectively the compound's potential from competitors. An EC study then provides added confidence to EBPs engaging with investors that their molecule may reach its next milestones and eventually provide returns on investment. In such context, early contextualization of a treatment effect may offer a competitive advantage to EBP due to better contextualization of the compound with EC information compared with competitors with similar results, enabling them to attract more funds for the future development of their therapies. Similarly, an EC study can also be of use for larger companies who need to convince analysts about the potential of their assets since their stock market performance are directly affected by trial results [40,41].

Other than external financial stakeholders, companies need to convince investigators and patients to participate to further trials, often over similar therapies in development. The well-known challenges in patient recruitment have a substantial financial impact on drug development and sponsors' finance by extending timelines or requiring additional sites [42,43]. Investigator and patient engagement and participation are therefore critical factors in delivering trials on budgets. While the primary motivations for patients to participate in clinical trials are the hope for a cure and the advancement of disease knowledge [44], it is also crucial to consider the patient's interest in avoiding ineffective or suboptimal treatments. Highlighting potential benefits to patients against SoC by including an EC study in the early phase evidence package could address this and be a strong supportive factor in obtaining their participation by adding scientific credibility and evidence strength.

Limitations of EC studies for clinical development

Despite EC studies providing clear benefits to inform clinical development and the continuous enhancement of RWD, limitations exist and must be acknowledged.

Technical enablement

EC studies rely primarily on RWD that need to be generated, captured and stored in sufficient details and quality, which can pose a problem in environments where the technology is not mature enough to support such process. EMR adoption has been increasing for the past decade with the most developed countries having a >85% adoption rate [45], but many countries are lagging behind [46,47]. Moreover, the existence of an EMR is important but not sufficient to enable an EC study as they require both larger data breadth and depth than most observational RWE studies to enable a robust treatment effect adjustment based on many baseline covariates. Common parameters used to build the EC cohort include for example detailed patient characteristics and extensive tumor profiling, treatment history and details on actual treatments with sufficient follow-up information, treatment response information based on standard response criteria, safety information, etc [20]. Within a hospital, the IT system is often siloed and datasets hence require enhancement by linking different data sources. Across sites, standard heterogeneity and varying level of data capture is another hurdle that necessitate the creation of a common data model [48]. From a data privacy perspective, EC studies can also be more complex as de-identified patient-level data from the different sources needs to be transferred to a secured server in order to be pooled before any analysis is performed to properly balance the cohort; whereas in other types of RWE studies (e.g., treatment patterns and outcome analysis), a 'hub and spoke' approach, where data are analyzed on sites and only results are aggregated centrally, can be used [49]. Furthermore, especially in the European context, each country also has their own regulatory requirements, hospitals their own processes, making multisite analyses even more complex. While currently these challenges are tackled on an individual basis, in the future, data alignment initiatives such as implementation of common data standard (e.g., OMOP [50]) are among possible solutions.

Statistical considerations

EC studies are conceptually complex designs that need sophisticated analysis considerations to mitigate inherent limitations related to nonrandomization and nonconcomitant comparisons. As such, they require careful design and rigorous evaluation, which represent a significant extra workload for a study that must be carried in addition to activities related to the conduct and analysis of the SAT. A well-thought methodology is all the more important since the most common causes for EC rejection as supportive evidence in EMA and FDA submissions are related to study design and selection biases, such as heterogeneity between patient populations, differences in outcomes assessed or missing data on potential confounders [20,35]. Inappropriate design and statistical analysis that does not allow to adjust major sources of bias are a common grief. Early-phase EC studies might not need to enforce criteria as strict as regulatory ones, but the impact of less stringent factors needs to be assessed and acknowledged. EC studies would also not help to counter results suggesting a substantial treatment effect just by random chance and the treatment effect difference would still be overestimated [20]. Even if confounding is fully addressed, differences in end point definitions between clinical trials and RWD can still introduce bias. For example, real-world progression-free survival may differ from clinical PFS due to less frequent imaging, variable documentation, and reliance on clinical judgment rather than standardized assessments [51]. Similarly, objective response rate in RWD is often based on physician notes or radiology summaries, which lack the rigor and consistency of RECIST 1.1 criteria used in trials [30]. These discrepancies underscore the importance of carefully evaluating end point definitions when designing EC studies and interpreting their results [52]. To help mitigate these differences, blinded adjudication can be employed to standardize the assessment of key end points across both trial and RWD populations. By having independent reviewers assess outcomes without knowledge of treatment assignment or data source, this approach enhances consistency and reduces bias in end point interpretation.

The flexibility in design choices – such as matching methods, inclusion/exclusion criteria and end point selection – can also inadvertently introduce bias or be perceived as selectively favorable if not transparently managed. As the use of EC studies becomes more widespread, stakeholders are becoming increasingly discerning about their methodological rigor. There is already a substantial body of literature outlining best practices for EC cohort design, and with growing familiarity, the target audience is more likely to scrutinize the assumptions and analytic choices behind each study. To maintain trust and ensure EC studies are used to evaluate potential rather than simply to showcase it, transparency is essential. Pre specification of analytic plans – including matching algorithms, end point definitions and sensitivity analyses – can help mitigate concerns around selective reporting and reinforce the evidentiary value of EC studies.

Finally, unobserved confounding caused by unknown prognostic factors can lead to inaccurate effect estimates and should be addressed via sensitivity analyses [25]. Hence, the role of an experienced real-world statistician cannot be overestimated in the setting of EC studies.

Conclusion

In conclusion, the unprecedented number of molecules in development creates an urgent need best evidence generation framework that can inform sound strategic decisions about which therapies to progress from early-phase. EC studies are a possible approach to partially de-risk clinical development by addressing the limitations of current pre-pivotal SATs. By providing insights on a molecule's performance against actual SoC applied in the real-world practice and potential competitors, EC studies enable pharmaceutical companies to identify the most promising compounds at early development phases. This early benchmarking empowers companies to make earlier and better substantiated decisions in the development process, particularly when randomized designs, which remains the gold standard in principle for clinical testing, are not feasible or suitable. EC studies can help to address the systemic issue of inefficient therapies consuming significant capital in later stage development and play a key role in refining a molecule's value proposition, which is particularly important for EBP who need to stand out from a crowded field to attract further funding.

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Summary points

- External comparator (EC) cohort studies offer a cost-effective and operationally efficient way to contextualize results from single-arm trials, especially in early-stage drug development where randomized controlled trials are not feasible.
- EC studies are increasingly accepted by regulatory bodies like the US FDA and EMA, with rising inclusion in health technology assessments and new drug applications.
- EC studies can help emerging biopharma companies – who often have limited resources – make better informed decisions about which compounds to advance.
- By mimicking randomized controlled trials, EC studies have the potential for enhancing investor confidence in early results, making them a strategic tool for attracting funding and differentiating from competitors.
- For larger companies, EC studies can de-risk portfolio decisions by identifying compounds with the highest potential for success, helping companies avoid costly failures in later-phase trials.
- EC studies support investigator engagement by offering clearer insights into a compound's potential benefits, which can improve later trial recruitment and participation.
- EC studies may help refine a compound's positioning by revealing comparative strengths and weaknesses, which can inform strategic repositioning and improve chances of success in later trials.
- Despite their benefits, EC studies require high-quality real-world data, sophisticated statistical design and careful handling of biases and confounders – making expert involvement essential for successful implementation.

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