



The mixed randomized trial: combining randomized, pragmatic and observational clinical trial designs

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Clinical trial designs often fail to deliver data that jointly satisfy evolving demands of both regulatory and reimbursement authorities. We propose a new multi-tiered trial design to integrate efficacy and effectiveness, and address the evolving needs of authorities. The mixed randomized trial allocates patients first to trial arm – randomized controlled, pragmatic (randomized) or observational – and then to treatment group – experimental, placebo, active comparator, best available therapy or standard of care. Trial arms may be staggered over time to reflect the current state of randomized and non-randomized data of the experimental drug, and thereby still prioritize safety. At the same time, the mixed randomized trial allows for the collection of real-world data in a randomized setting, and thereby reduces selection bias.

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Drug regulators and reimbursement authorities are requesting different things from drug sponsors. Regulators typically look for a positive benefit-to-risk ratio in a relatively restricted patient population from which they will conclude whether or not a drug merits being made available to patients. Payers, by contrast, look for reassurance that what has been shown in controlled clinical trials also translates into the real world, and is, broadly speaking, good value for money. Payers may also be burdened with cost-effectiveness thresholds and budgetary constraints, restricting their ability to grant reimbursement. These differing (and evolving) perspectives often necessitate having to consider a variety of clinical end points, comparators and patient populations. Currently, drug sponsors tend to separate regulatory and payer perspectives by collecting evidence for each at separate stages of the clinical development program. Despite attempts to harmonize evidence in preliminary scientific advice meetings, these two different perspectives

are rarely addressed in a truly integrated manner [1].

Reimbursement authorities in modern times typically require more than just placebo-controlled regulatory data from explanatory randomized controlled trials (RCTs) [2]. Rather, they also seek comparative effectiveness data from a wider, real-world setting, where the focus is on comparing the new drug with a standard of care (SOC). Head-to-head, active comparator RCTs are not typical for marketing authorization (MA), and they are also not usually favored by sponsors. The current tendency is to use supplementary evidence from post-approval, less well-controlled studies. These include pragmatic (randomized) trials, prospective observational trials and those with historic controls (Figure 1). Pragmatic and observational trials are likely to be conducted after pivotal RCTs for MA are completed. Collecting real-world data from such trial types, or via registries after Phase III development, inevitably leads to a delay in securing reimbursement.

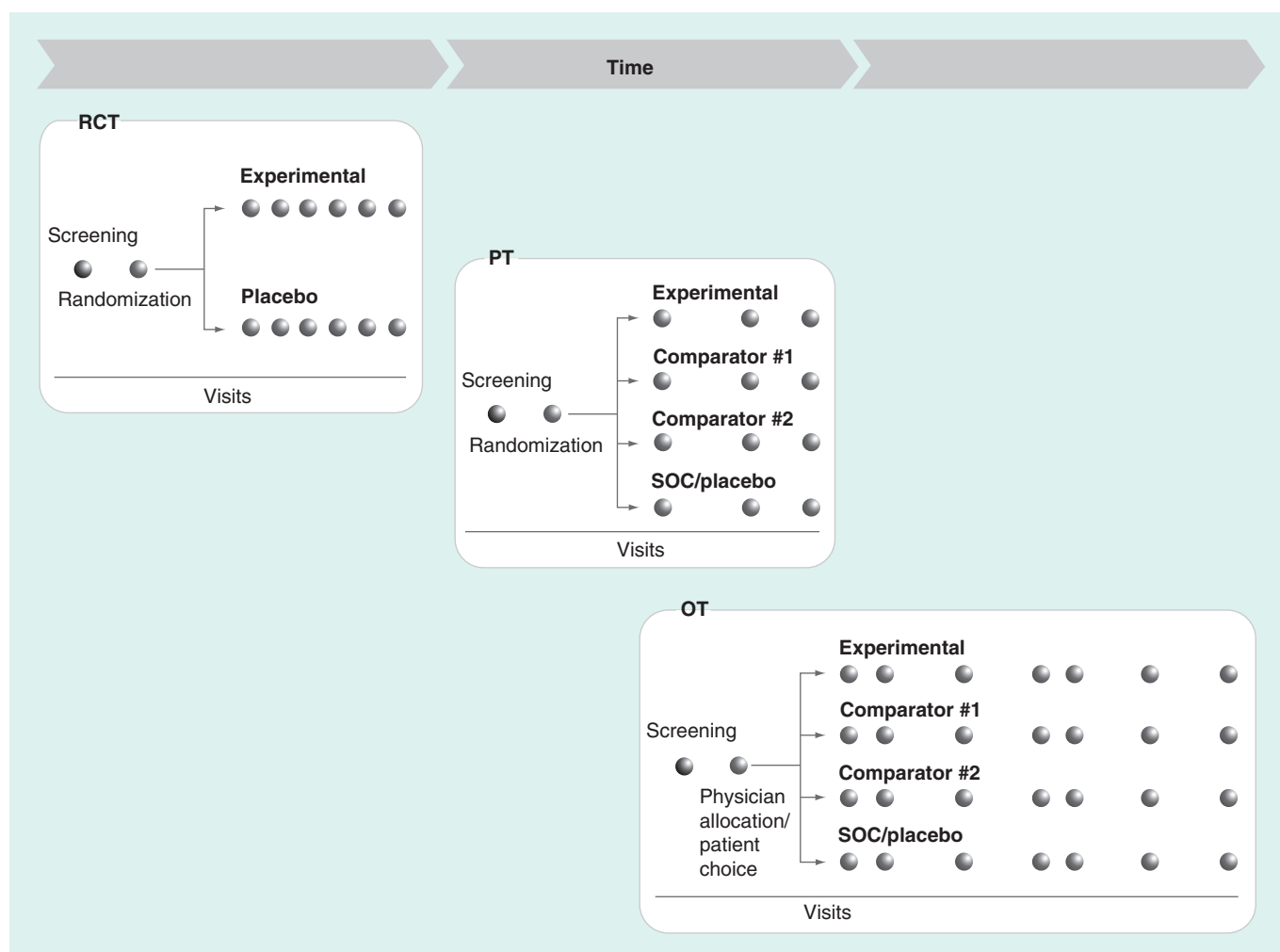


Figure 1. A typical late phase clinical development program.

OT: Observational trial; PT: Pragmatic trial; RCT: Randomized controlled trial; SOC: Standard of care.

Comparing RCT with non-RCT evidence

Sponsors often collect real-world data in order to satisfy safety concerns that regulatory authorities may have post-Phase III or to secure reimbursement from payers. Additionally, payers may request data that demonstrate cost-effectiveness, along with comparative effectiveness, against currently available therapies. The lack of availability of real-world data earlier in development is a major weakness in many reimbursement submissions. Sponsors typically prioritize the earlier MA over reimbursement approval – the design and types of data collected at the Phase III stage typically reflect this. As such, reimbursement authorities often face a lack of evidence as to whether or not a sponsor's drug performs better than current alternatives in the real world.

Current approaches to analyzing comparative effectiveness data obtained outside robust RCTs can lead to biased treatment comparisons, which rightly or wrongly, receive criticism from both regulatory and reimburse-

ment authorities. For example, it is problematic to compare observational trials with RCTs if the studies were conducted under different protocols – for example, different comparator treatments, patient populations, length of follow-up, primary end points and so on. Consequently, there has been considerable investigation into comparing treatment estimates between data from randomized and non-randomized trials [3–7]. Given the level of bias and uncertainty surrounding treatment estimates obtained from non-randomized, uncontrolled trials, treatment effects generally need to be more convincing (i.e., larger) than those observed from RCTs. More convincing treatment estimates might otherwise support more successful reimbursement.

New designs

New clinical trial designs that meet modern evolving expectations coming from both regulatory and reimbursement authorities are highly desirable [8–10]. There

have already been calls for more pragmatic trials, given their greater generalizability to the real world [11]. Trial designs that integrate both RCT and real-world data would be better placed to address some of the challenges associated with analyzing comparative effectiveness data, especially if combined with prospectively defined analyses.

Some progress has been made in the area; however, none have gained widespread acceptance and most are in their infancy in terms of development [12–19]. Such designs have typically focused on individually adapting either explanatory RCTs, pragmatic trials or observational trials. Some argue that there are no hard distinctions between trials designs, for example, between explanatory RCTs and pragmatic trials; and that efficacy and effectiveness exist along a continuum [20,21]. To some extent, current RCTs endeavor to address both ends of this continuum by, for example, using the intention-to-treat approach. Nevertheless, the intention-to-treat approach is a somewhat limited attempt to reflect the differences between how patients respond in a real world compared with a trial ‘per protocol’ population [22].

In order to better address the needs of regulators and payers, and to utilize modern experience in clinical trials, we propose a new multi-tiered trial design – the mixed randomized trial (MRT). The MRT combines aspects of the three main trial types: RCTs, pragmatic (randomized) and observational. Its principle aim is to prospectively bring together randomized, controlled data and real-world data under one umbrella. The MRT has the potential to deliver a combined data package that meets the evolving demands of regulators and payers faster than separate individual trials.

Methods: MRT design

We propose the MRT specifically to address the challenge of combining randomized and non-randomized data. The MRT is a single, integrated design, albeit multi-tiered, with different trial arms (Figure 2). Typically, the MRT would include the following arms, which would all be prospectively defined:

- Trial arm #1 – RCT;
- Trial arm #2 – randomized pragmatic trial (PT);
- Trial arm #3 – observational trial (OT).

MRT trial arm #1 is the standard explanatory RCT, with the usual procedures that would be undertaken in a typical Phase III trial. The PT arm would equate to a pragmatic trial encompassing a range of pragmatic elements [18]. Of note, here is that we have assumed the MRT’s PT arm incorporates randomization of patients

to study treatment. Randomization of patients to treatment groups in the PT arm, while desirable from an internal validity perspective is, however, not wholly necessary. Finally, we consider the OT arm to be one that is essentially non-interventional (e.g., a patient registry without fixed visit schedule).

The MRT design combines elements of trials conducted at the latter end of clinical development with those conducted at the early stages of the post-approval period (e.g., Phase IV). It also includes elements of the two-stage hybrid design and expands on the doubly randomized preference trial [16]. To our knowledge, the MRT design outlined here has not been previously proposed. It also presents with some distinct advantages and challenges compared with standard Phase III practice, summarized in more detail below and in Box 1.

Design elements

Allocation of patients

Patients would first be randomized to one of the three trial arms. Those randomized to the RCT or PT arms would then be randomized again, this time to study treatment (e.g., experimental, placebo, SOC or active comparators including best available therapy). This ‘twin’ randomization would be conducted similarly to that performed in a typical standalone RCT. Indeed, the randomization of patients to trial arms is broadly similar to the use of a stratification or blocking factor.

Those randomized to the OT arm would receive treatment as per local clinical practice and at the discretion of the physician/patient (Figure 2). Randomization would ideally be performed under blinded conditions; however, full blinding at the trial level would be problematic due to the unique design elements of each arm (e.g., fixed visit schedule in the RCT arm). Study investigators would also need to know if a patient was randomized to the OT arm, so that they could allocate the patient to a suitable active treatment (e.g., experimental, active comparator[s], SOC). Efforts should be made to maintain blinding at the trial arm level, such as with the use of blinded assessors. This is a relatively common approach in RCTs where unblinding of patients or treating physicians is a potential risk. The use of objective end points (e.g., blood/biomarker concentrations, ambulatory tests, pulmonary function tests, relapses, death) could also help to minimize potential bias. The comparison of interest within an MRT lies between treatments rather than trial arms, and thus, it is not wholly necessary that investigators and patients remain blinded to trial arm allocation. Nevertheless, reducing treatment preference, and resulting bias, demands keeping both trial arms and treatment groups blinded where possible. Blinding to

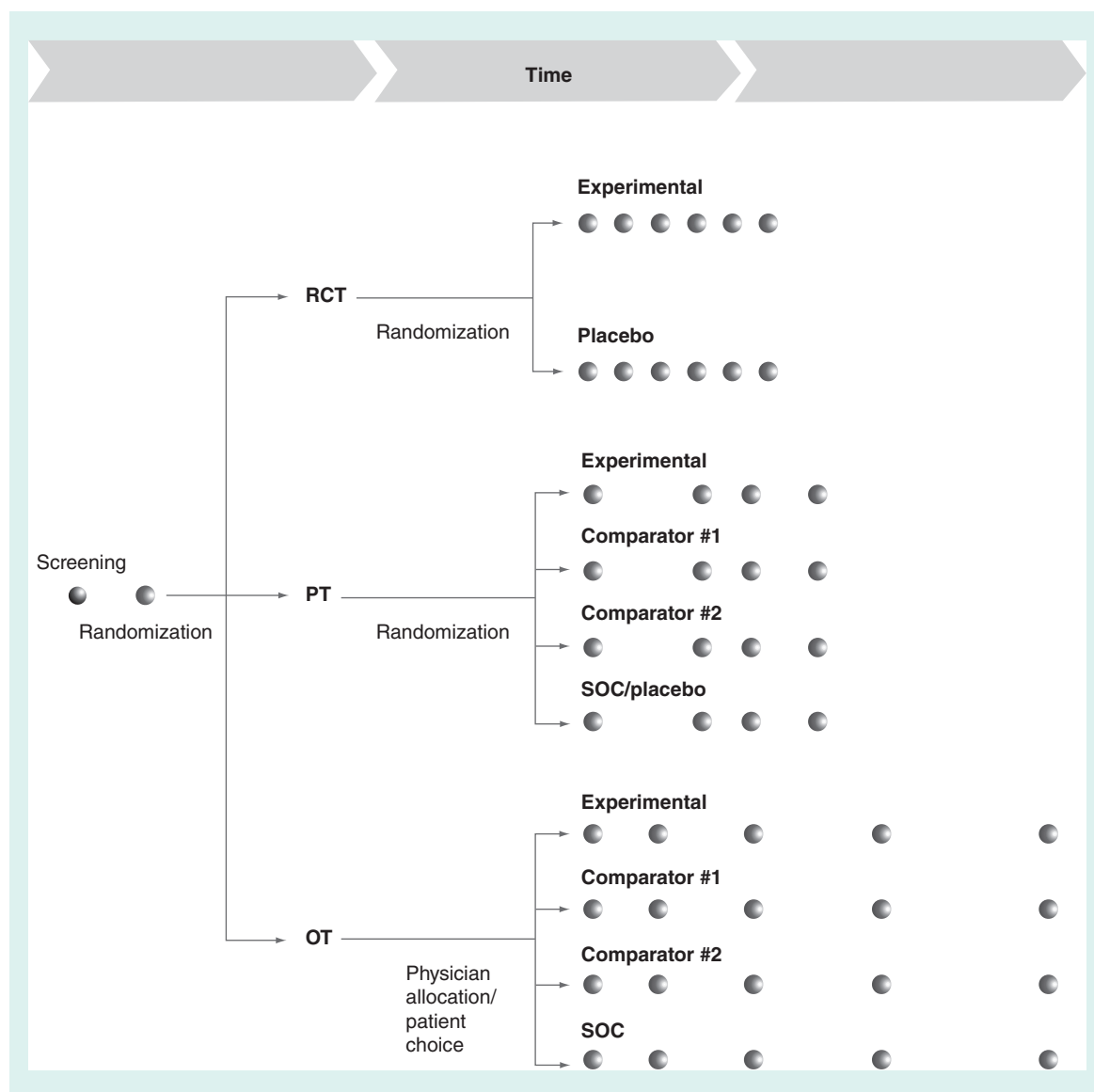


Figure 2. Mixed randomized trial arms and treatment groups.

OT: Observational trial; PT: Pragmatic trial; RCT: Randomized controlled trial; SOC: Standard of care.

treatment group within each trial arm would in any case be performed as standard practice.

The randomization ratio of patients to each trial arm could be chosen as a simple balanced assignment (i.e., 1:1:1), but there are no obvious barriers to using other ratios with the MRT design. It could, for example, be beneficial to allocate patients to a 1:3:4 (RCT:PT:OT) ratio. The optimal ratio should consider factors such as the balance between the amount of currently available controlled and uncontrolled data. With the multi-tiered MRT structure, that is with three simultaneous and independently running trial arms, the randomization ratio could also be adapted (e.g., from 1:1:1 to 1:3:4) at planned time points. This would reflect the increasing knowledge of the drug's

efficacy and safety profile by proportionally adding more patients to the PT and OT arms. Furthermore, there may be a need to maximize collection of comparative effectiveness data from important comparators (e.g., in cases where a reimbursement authority has required data on a particular SOC or best available therapy).

Alternatively, the patient randomization ratio can allow for appropriately minimizing the number of patients in the PT and OT arms (in the extreme example, with 1:0:0) where a safety risk is unacceptably high with an otherwise unapproved drug. Such a ratio can, for example, be used at the beginning of an MRT so as to stagger the commencement of the RCT, PT and OT arms, over time (Figure 3). The timing of

the initiation of the PT and OT arms would thereby reflect the current state of the available controlled and uncontrolled data, and would commence following some form of MA. For example, it might be reasonable to start with a 5:1:0 ratio, and then subsequently to progress toward 1:3:4, over the course of months or years.

Trial conduct

Each of the trial arms would be conducted as per standard practice. Patients in the RCT arm would undergo a (typically) wide range of clinical assessments at scheduled visits. Despite being similar to the RCT, the PT arm would allow patients to undergo a less rigorous schedule, choosing to focus on collection of key safety and efficacy data. Patients randomized to the OT arm would also undergo a similar, or less frequent, follow-up regimen as per the patients randomized to PT, and would be allocated treatment according to local treatment guidelines or physician/patient preference. Under certain conditions, this could include the active (experimental) therapy, although it is unlikely that this treatment would be available at MRT onset. It would undoubtedly be preferable to have the experimental treatment group available as soon as possible in the OT. Therefore, in the cases where the RCT, PT and OT arms were staggered over time, there should be a plan for an initial, conditional MA (Figure 3) [23].

Statistical planning & analysis

Careful and thoughtful planning of the multi-tiered MRT structure is paramount. The MRT's primary efficacy end point should be chosen to best match the needs of both regulators and payers – optimally following joint scientific advice. In any case, the MRT should be statistically powered on the treatment comparison of most clinical interest. Sample size calculations could be more challenging than for a standard RCT, especially if inter-trial arm variability is considered with respect to the expected treatment effect size. Nevertheless, a typical MRT would enroll substantially more

patients than a standard RCT and would thereby address this issue.

Efficacy and safety data from each of the three MRT trial arms would be combined in a formal, pre-planned, statistically appropriate manner in order to support regulatory approval. Statistical adjustment for the effect of the trial arm should be made via the inclusion of a trial arm term (e.g., as a main effect) in the primary-end point analysis. A single, prospective statistical analysis plan, with such issues carefully described, should be agreed before any unblinding. Interim analyses may also be desirable before initiating the PT or OT trials arms, or for adaptations of the randomized treatment allocation ratios within the RCT and PT arms. For example, a placebo arm might be dropped if there was sufficient interim data to indicate superior efficacy of the experimental arm. Indeed, most common Phase II or III trial adaptations (e.g., 'play-the-winner' design) can be implemented within the MRT framework [24]. Health economics data (e.g., quality of life) would also typically be collected in some, if not all, trial arms of the MRT in order to support reimbursement submissions.

Timing for MA & reimbursement

The MRT would be most valuable when conducted after initial Phase III development, once the safety, efficacy and tolerability of the investigational drug has been tested within a controlled setting. The MRT could then be introduced in Phase III (e.g., replacing a second pivotal Phase III trial) with the aim of achieving full MA. To this end, a staggered approach could be made (Figure 3). For example, interim data from the RCT arm could be used to obtain a limited (conditional) MA. This could then be formally combined with data from the PT using standard analytical techniques in order to obtain wider regulatory approval and conditional reimbursement via an adaptive licensing procedure. Data from the completed PT and OT arms could then provide the necessary real-world comparative effectiveness data to allow for full reimbursement. The optimal timing of the MRT within

Box 1. Advantages and challenges of the integrated design.

Advantages

- Prospectively defined framework for comparing controlled and uncontrolled data
- Pathway for regulators to view efficacy and effectiveness side-by-side
- Broader patient population and thereby greater generalizability to real world
- Increased focus on active comparators
- Reduced expense and timelines by reducing number of trials

Challenges

- Complexity and more extensive operational planning
- Patient exposure to experimental treatment in an uncontrolled setting
- Complexity of combining data from different trial arm types
- Continued issues of bias in pragmatic and observational settings
- An as yet unknown trial design

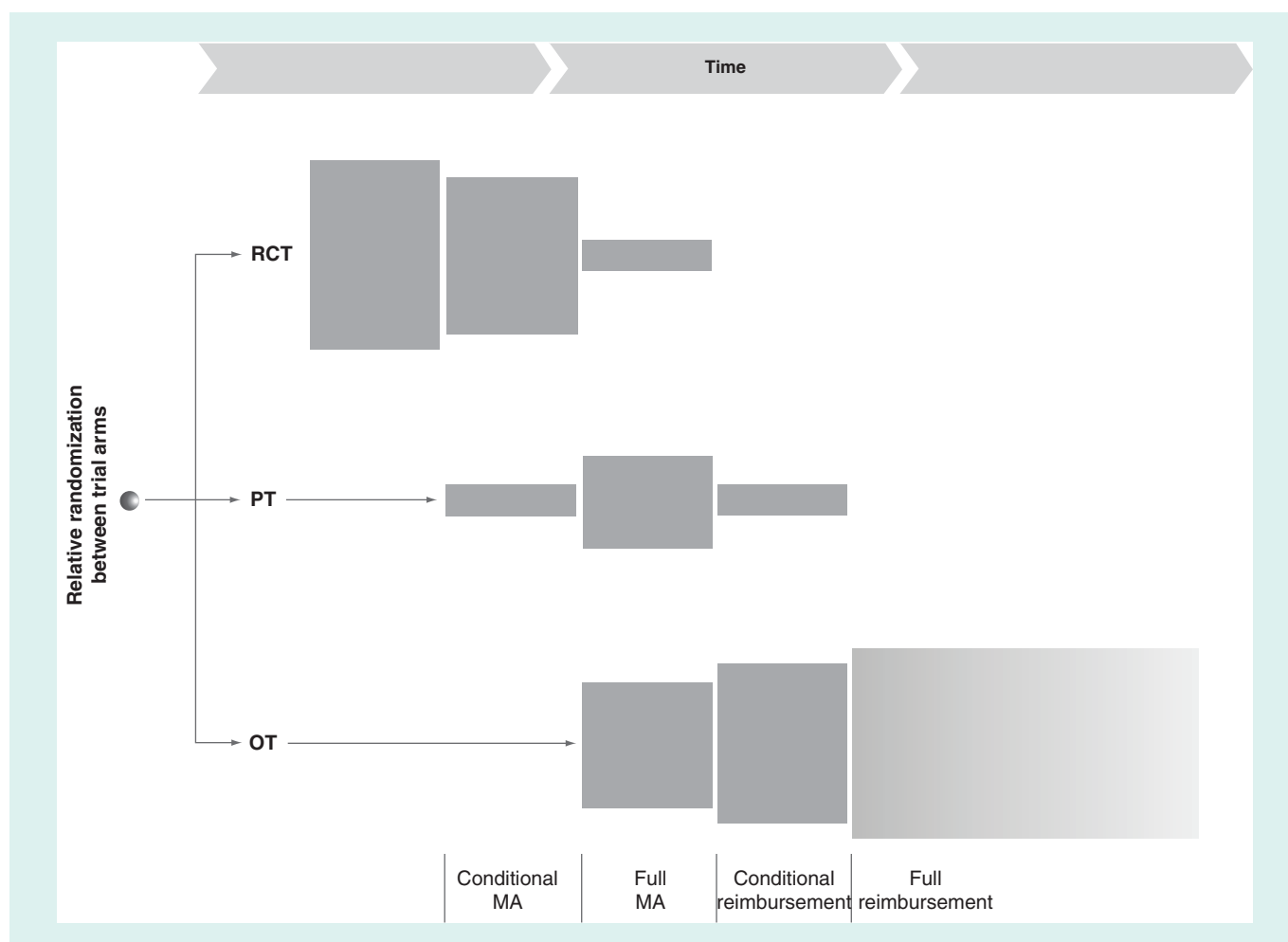


Figure 3. Mixed randomized trial staggered randomization of patients over time.

MA: Marketing authorization; OT: Observational trial; PT: Pragmatic trial; RCT: Randomized controlled trial.

the overall clinical development and reimbursement program would presumably depend on the therapeutic area, currently available RCT/comparative data and market conditions.

Advantages of the integrated design

The MRT offers distinct advantages compared with standard Phase III clinical trial designs.

Real-world data

As discussed, comparing the results of trials conducted using different patient populations between pre- and post-MA studies can be a considerable challenge [25–28]. The relatively simple act of randomizing patients to each trial arm (RCT, PT or OT) within a multi-tiered MRT structure would ensure that baseline patient characteristics are balanced across trial arms. Moreover, it puts into place a prospectively defined framework under which randomized controlled data can be directly compared with uncontrolled, observational

data. This has the benefit of allowing for the identification and quantification of biases associated with data from controlled-trial versus real-world conditions. Comparing data across these conditions from within the MRT structure should thereby be more acceptable to reimbursement authorities, and payers, faced with the challenge of interpreting real-world data, can quantify and assess the uncertainty by comparing RCT results with those from the PT and OT arms.

Pathway to integrated data for regulators & payers

The MRT provides authorities with an upfront commitment to obtain real-world safety, efficacy and comparative effectiveness data. Currently, comparative effectiveness data are often provided to payers using indirect comparisons between treatments – that is, not from head-to-head, active-comparator trials. These sorts of comparisons are problematic and prone to bias, and although requested, are open to scrutiny from the

reimbursement authorities. The MRT provides a greater provision for direct treatment comparisons, and thereby to clinical data from a broader and comparable set of patients in controlled and real-world clinical settings.

Patient population

The restrictive nature of patient populations enrolled in Phase III trials has been noted by regulatory authorities and the pharmaceutical industry [29]. Authorities have implemented guidance to push for a broader range of patients in clinical development programs (e.g., pediatric investigational planning) [30]. Here, a wider range of patient demographic and disease profiles is envisaged in the MRT as compared with traditional RCTs. This would increase the generalizability of the data to the wider disease population, and therefore, increase the likelihood of acceptance by both regulatory and reimbursement authorities. In particular, due to the larger size of the MRT, it would allow for a more robust assessment of the effectiveness of the drug within subgroups, as well as in the detection of safety signals.

Active comparator choice

Historically, the choice of an appropriate active comparator at a Phase III stage was determined primarily by regulatory requirements. Placebo has traditionally been used as the standard non-active comparator whenever ethically possible. More recently, however, the choice of comparator is being determined by payers and there is considerable variation in the active comparators of choice across multiple regions/countries. This is because payers in different regions/countries have different standards of care available to them on the market. The MRT structure allows for a wider range of comparators to be included in an integrated study, which is a significant improvement over standard Phase III RCTs. The MRT has, for example, the ability to capture data from new active comparators within its OT arm. Randomization in the RCT and PT arms can also be reasonably adapted to incorporate active comparators as required.

Financial

One of the intentions of the MRT is to remove the necessity of conducting multiple Phase III/IV trials. Although larger (in terms of patient numbers) than any clinical trial of a single type, the MRT could result in an overall reduced setup and running cost. Given the reduced levels of follow-up and monitoring in the PT and OT arms (compared with the RCT arm), it might well be expected that the MRT would result in lower average per-patient costs. Once a drug is determined to be sufficiently safe, a patient randomization ratio favoring the less expensive PT and OT arms could be uti-

lized. Key efficacy and safety data (used specifically for an initial MA) could be collected at a lower financial burden, as compared with a standard RCT. Finally, the MRT's multi-tiered approach, as compared with the standard sequential Phase III/IV clinical development process, could lead to a considerable reduction in the time required to obtain MA and reimbursement. This could result in faster patient access to new drugs.

Challenges of the integrated design

Complexity

Conducting an MRT would require more careful planning and preparation of resources, as compared with a standard Phase III RCT. The individual complexities of each of the separate trial arms would not be reduced by the simple act of randomizing patients under a single trial protocol. Statistical powering of the MRT, when (and if) to perform interim analyses and how to combine data across the trial arms, would all be non-trivial challenges. Determining the optimal randomization ratio of patients to each trial arm would also be far from trivial, and is a central exercise to the multi-tiered and staggered approach of the MRT structure. An additional complexity arises with the operational running of the trial arms in parallel, as compared with in series (as per current standard practice). Overall, the combined data may also provide additional interpretation and understanding challenges to the regulatory/payer reviewers, especially if the efficacy or safety signals differ by trial arm.

The MRT would certainly require more adept planning and preparation of resources on behalf of the sponsor, compared with a single, standalone Phase III RCT. The costs of implementing the MRT could also well exceed the cost of any single trial implementation happening in series. Furthermore, a sponsor could undergo a significant commercial loss with any failed MRT, compared with an 'equivalent', negative Phase III RCT. The complexity of a new trial design will always have challenges in the beginning, and may need to be adapted with the learnings in conjunction with regulators and payers.

Enrolling patients

Exposing patients in an experimental treatment group in an uncontrolled setting (i.e., in the PT and OT arms) adds risk over and above a standalone RCT. Some investigators might be hesitant to expose their patients to an untested drug, and resistance from ethics and regulatory bodies could be expected [31]. In order to address these concerns, patients randomized to the PT and OT trial arms could be blocked from being allocated experimental treatment at study onset, essentially delaying allocation to the experimental arm until

sufficient interim RCT data become available. Such a delay would, for example, allow a data review board to evaluate all safety data collected from within the MRT to date. Recommendations from the review might well reassure regulators that expanding the (unapproved) drug to a larger, observational population (i.e., the PT and OT arms) would be ethically sound. Any delay in the onset of recruitment to the experimental treatment group would, however, weaken the value of the data. This would be particularly true if either the available patient population or treatment practices (e.g., SOC) change rapidly over time.

Generalizability

The inclusion and exclusion criteria of the MRT would have to be less strict than its RCT counterpart. In the ideal circumstance, inclusion criteria would be as wide as in any standalone observational trial. While shortcomings of narrow entry criteria are certainly valid with respect to external validity, convincing some ethics committees to expose a wider range of patients to a potentially unsafe or ineffective drug could be difficult [18]. Sponsors usually wish to optimize a study's success, which is often achieved with a relatively homogeneous disease population. Nevertheless, in the wake of safety concerns arising with currently marketed products, regulator and payer demands dictate testing drugs in a wider range of patients [32]. Given that the MRT would be conducted toward the end of Phase III development, exposure of a novel treatment to a wider patient population would seem to be a justifiable risk in contemporary clinical research. Planned interim analyses could be used to allow for widening of patient inclusion criteria over the time course of an MRT.

There may be concerns regarding the generalizability of the results from combined data from different trial designs. Such concerns could be partially alleviated by measuring end points in a consistent manner between each trial arm. The problem of synthesizing results from multiple trial sources is a problem that authorities face on a regular basis [33]. At the very least, the multi-tiered MRT structure brings an integrated and prospectively planned approach to this dilemma.

Bias

While the MRT allows for an integrated assessment of many of the biases outside a strict RCT setting, it cannot completely remedy a situation in which considerable bias is present or when a particular bias affects all trial arms. Attrition bias (e.g., patient drop-out/withdrawal) would still pose a serious challenge to the interpretability of the MRT data regardless of the multi-tiered structure. This would particularly be the case if the drop-out rates varied between trial

arms. Selection bias typically present in observational trials will not disappear from the OT arm because it has been incorporated into an MRT structure.

The issue of greater bias in the PT and OT arms is part of a wider between-trial arm heterogeneity issue. Results that differ between the trials arms might be challenging to resolve. In these instances, the natural inclination of regulatory and reimbursement authorities may be to place greater emphasis on the RCT results over those from the other two trial arms. Nevertheless, there is far greater scope to resolve trial arm differences observed within the MRT structure as compared with trying to resolve differences across completely separate trials.

Within-trial arm variability might also be expected – more so in the PT and OT arms due to lower control of the patients' adherence to treatment and follow-up. The increased risk of bias from both the between-trial arm and within-trial arm variability should generally lead to higher overall sample size requirements as compared with pure RCT approaches. As such, reviewing authorities may be tempted to down-weight the PT/OT results (either in a formal statistical manner or in their interpretation) if a concerning level of heterogeneity was observed. How a regulatory or reimbursement authority might judge disparate results between the trial arms could depend on whether the divergence occurred within safety, efficacy and/or quality of life outcomes.

Discussion

Reimbursement authorities require real-world evidence in addition to that from RCTs, while regulatory authorities generally focus on evidence obtained under controlled (and often artificial) clinical conditions. This variation in focus arises from the differing perspectives and evolving needs that drive decisions from the two types of authorities. Drug development is, in any case, required to satisfy both needs. The challenge is when and how to efficiently provide authorities with the necessary data. It is inherently inefficient to obtain the evidence from multiple clinical trials separated in time by months, if not years. Moreover, the differences between regulatory and payer perspectives, as with RCTs and pragmatic trials, and efficacy and effectiveness, are not black and white, but rather lie along a continuum [20,21].

The pharmaceutical industry should be designing and conducting clinical trials that incorporate elements that reflect the real world while retaining much of the robustness and internal validity that RCTs have been providing over the past decades. The MRT structure provides a formal framework for the collection and analysis of real-world data in a randomized setting. The proposed study design seeks to jointly address the concerns of regulators and payers. Importantly, the MRT

structure facilitates the current industry trend of conditional MA, with full MA and reimbursement granted upon successful delivery of real-world evidence.

The MRT has the potential to reduce both the costs and the time to regulatory approval and reimbursement. This may feasibly be done by obtaining data under a single, prospectively planned, integrated MRT protocol, rather than across multiple separate Phase III/IV studies.

Fear of untested trial designs will undoubtedly play a part in whether or not a sponsor would choose to implement an MRT. Nevertheless, although slow to adopt innovations in clinical trial design, pharmaceutical development needs to address the evolving requests for data under both RCT and real-world designs. The MRT has substantial advantages that facilitate the collection, combining and contrasting of RCT, and observational data. It also offers a platform upon which to incorporate adaptive patient randomization ratios. The adaptive ratios could initially protect patients from experimental, real-world intervention, while also providing faster access to a drug once controlled data become available.

The MRT's multi-tiered approach provides a framework for a new type of clinical trial. Despite offering considerable advantages, challenges remain in its implementation, and operational details remain to be clarified, especially in regard to the timing of the introduction of any experimental, unlicensed, treatment. What is in any case clear is that as demands on clinical data evolve, so must clinical trial design also continue to evolve.

Future perspective

Payers, given their clear and strong mandates to lower drug costs, are coming under mounting price pressures. They are increasingly concerned with the uncertainty of what they are paying for, with a specific focus

on added value for their own country's demographic. This has brought an increased demand for real-world evidence. The focus toward real-world evidence will presumably continue over the next 5–10 years, and demand different ways of thinking about clinical trials. It will also demand new trial designs and statistical methodologies to combine real-world data with more controlled trial data. The future will most probably place more responsibility on the shoulders of pharmaceutical companies to ensure their drugs have a greater added value within specific populations. Payers will reserve the right to adapt, and possibly reverse, MA and reimbursement for those drugs that do not stand the test of growing real-world evidence. New trial designs and statistical methodologies will thereby also need to adapt.

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Executive summary

Background

- Current clinical development practice is often insufficient to satisfy both regulatory and reimbursement authorities.
- New trial designs are needed to satisfy evolving demands, especially those that provide the ability to compare and contrast efficacy with effectiveness.

Mixed randomized trial design

- We propose an integrated trial design randomizing patients first to trial arm – randomized controlled, pragmatic (randomized) or observational – and then to treatment group – experimental, placebo, active comparator or standard of care.
- The mixed randomized trial (MRT) structure has the potential to combine randomized, controlled data with real-world data in a prospectively defined manner.
- The MRT structure has the potential to reduce bias and cost as compared with running multiple independent clinical trials.
- The key challenges are judging when the data are sufficient to justify giving a new drug outside strict clinical trial controls, and the increased planning required for a more complex clinical trial design.

Conclusion

- The MRT could be sufficient to meet both regulatory and reimbursement requirements for success.
- Evolving demands from authorities are already leading to new trial designs like the MRT.

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