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Perspective

Considerations driving the choice in clinical trial design of cell and gene therapy products: weighing convenience versus necessity

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A B S T R A C T

Because of small patient populations, lack of effective therapies, and complicated treatment protocols, advanced therapy medicinal products (ATMPs) for rare diseases are often licensed based on evidence generated outside of a "gold standard" double-blinded, randomized controlled trial (RCT). The lack of important bias-reducing features in non-RCTs can present uncertainties for regulators and health technology assessment bodies, making choice of trial design a critical decision for developers. This "Meeting of the Minds," co-hosted by the Alliance for Regenerative Medicine, the International Society for Cell & Gene Therapy and ATMP Sweden in December 2024, set out to create a structured framework that provides clarity on when deviation from an RCT is necessary and should be acceptable, and on how alternative study designs such as a single-arm trial or unblinded RCT may be justified. Through multi-stakeholder engagement and discussions of case studies, a "trial-design decision tree" was generated that can help guide developers and healthcare decision-makers through a stepwise approach to contemplating deviation from an RCT. Although not exhaustive, three clinical scenarios surfaced where departure from a blinded RCT appears warranted: cases where the experimental treatment is expected to have high efficacy but the enrollable patient population is too small, cases where there is no effective standard of care and patients assigned to placebo would experience significant disease progression during the trial and cases where subjecting the control group to complex, burdensome and potentially risky protocols in the interest of blinding would impose unacceptable burden on patients.

Key Words: ATMP, randomized controlled trial, rare disease, single-arm trial.

Introduction

Achieving therapeutic progress for rare diseases is inherently challenging. The natural history of such diseases is often poorly understood, phenotypic and genotypic diversity can exist within a single disorder, and small patient populations make clinical trial enrollment difficult. Furthermore, drug development tools such as biomarkers and clinically meaningful endpoints are often lacking. These challenges add an extra layer of complexity in a context where, though collectively affecting up to 6% of the global population [1], less than 5% of patients with rare diseases currently have an effective treatment option [2].

Because 80% of rare diseases have a genetic component [2], they are well-suited to being treated with cell and gene therapies, often referred to in Europe as "advanced therapy medicinal products" (ATMPs). The European Medicines Agency (EMA) defines ATMPs as "medicines for human use that are based on genes, tissues, or cells" [3]. Although double-blinded and randomized controlled trials (RCTs) have become the "gold standard" for demonstrating efficacy in drug development and decision-making [4–6], there has been significant use of non-RCT data in ATMP licensing worldwide. In Europe, 77% of available ATMPs have been licensed based on data from non-RCTs, and roughly 54% of ongoing gene-therapy pivotal trials are non-RCTs, with very similar numbers in the United States [7].

In both the United States and the European Union, regulatory authorities have increasingly acknowledged the unique challenges

A "Meeting of the Minds" hosted by the International Society for Cell & Gene Therapy (ISCT), the Alliance for Regenerative Medicine (ARM) and ATMP Sweden

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posed by rare diseases and ATMP development, particularly with regard to trial design and evidentiary standards. The Food and Drug Administration (FDA) and EMA share a common understanding of the ethical and logistical barriers to conducting RCTs in ultra-rare or rapidly progressing diseases, and both have accepted single-arm trials (SATs) as pivotal evidence in select cases. In doing so, each agency emphasizes the importance of contextual data—whether from natural history cohorts, previous clinical trials or high-quality real-world evidence—to support meaningful interpretation of SAT outcomes. Although both regulators encourage early and sustained dialogue with sponsors, the FDA has frequently leveraged its Accelerated Approval and RMAT (Regenerative Medicine Advanced Therapy) designations to enable earlier market access on the basis of promising non-RCT data, while requiring post-marketing confirmation [8]. The EMA, by contrast, typically imposes a higher upfront evidentiary threshold for full marketing authorization, though it too has approved multiple ATMPs—including autologous CD34+ cells transduced to express adenosine deaminase (Strimvelis, GlaxoSmithKline, London, UK) and atidarsagene autotemcel (Libmeldy, Orchard Therapeutics (Europe) Limited, London, UK) —on the basis of non-randomized evidence [9,10].

Table 1 summarizes all ATMPs (specifically, cell and gene therapies) approved by either the FDA or EMA between 2016 and 2024, including trial design type and number of enrolled patients. These examples illustrate the diversity of approaches taken on both sides of the Atlantic and the growing regulatory sophistication around evidence generation for advanced therapies.

Multiple factors can steer investigators and developers of rare-disease therapies away from a blinded RCT and, potentially, toward the use of an SAT. Aside from small patient populations and lack of an effective standard of care (SOC) for most rare conditions, it may be unethical to randomize patients to placebo when studying a severe progressive disease. In such cases, patients and families may refuse to enroll if placebo assignment is possible, whereas investigators and ethics committees may deem allocation to placebo unethical and clinically inappropriate. In addition, rare diseases often have short treatment windows relative to the time required to run an RCT, and the complex administration of many ATMPs can make blinding of an RCT unfeasible [6].

With an SAT, the combined lack of randomization (used to help ensure that study arms differ solely by treatment assignment at baseline) and blinding (used to ensure that arms are treated and evaluated identically during the trial) eliminate the two strongest bias-reducing features of a clinical trial design [11]. The absence of a randomized internal control group also makes it difficult to attribute causality to an effect of the investigational treatment [12]. As such, the use of SATs can present uncertainties for both regulators and health technology assessment (HTA) bodies in the European Union, the latter of which are tasked with exploring the clinical and economic added value of therapeutics and providing recommendations on their use and reimbursement in an EU Member State or region [13]. Hence, deviation from a blinded RCT (and movement toward an SAT) is a decision warranting thoughtful consideration.

On December 5, 2024, the Alliance for Regenerative Medicine (ARM), the International Society for Cell & Gene Therapy (ISCT) and ATMP Sweden co-hosted a "Meeting of the Minds" between academics, developers, regulatory representatives, HTA representatives and other key stakeholders (see Table 2 for full list of participants). The goal of the meeting was to address a key unanswered question in drug development for rare diseases: under what circumstances is deviation from the blinded RCT gold standard warranted? In addition, meeting participants briefly explored appropriate comparator data sources and methodologies for filling data gaps when SATs are deemed necessary.

Considerations Informing Choice of Trial Design

The Meeting of the Minds was motivated by the recognition that, while an increasing number of health authorities recognize that RCTs are not always ethical or feasible, a rigorous basis for determining when this is the case was lacking. With support from the literature [7,14–19], meeting organizers developed a framework (Figure 1) that provides developers and assessors with a structured way to think and talk about choice of clinical trial design. When contemplating key development program factors and their implications for trial design, consideration must be given to both the overall patient population (informed by the number of patients affected by a disease) and the trial-ready patient population (determined by the ease of identifying and enrolling diagnosed patients). The latter, along with the expected magnitude and time required to observe a treatment effect, has distinct implications for generating sufficient statistical power in an RCT. The urgency of the medical need (e.g., rapidly progressive disease versus stable disease) may inform whether there is sufficient time to conduct an RCT with crossover to active treatment at the end of the trial, whereas the treatment context (i.e., presence or absence of effective treatment alternatives, treatment burden and feasibility of blinding) may impact whether patients and healthcare providers would be willing to participate in a trial involving blinded randomization. As summarized in Figure 2 and discussed further in the section "Key Considerations when Contemplating Deviation from an RCT," careful breakdown of each of these factors informs the extent to which an RCT is feasible and ethical.

Case studies to illustrate the impact of development program factors on trial choice

Six case studies covering diverse rare-disease therapeutic areas (Table 3) served as vehicles for exploring how specific development factors weigh on the ethics and feasibility of different clinical trial designs. Special consideration was given to how these factors may make deviation from the RCT gold standard necessary versus simply convenient for developers. Discussion of cases adhered to the pre-competitive, interactive and non-binding nature of the meeting. Additional ATMP development programs have since been examined for their relevance to informing the choice of clinical trial design for rare diseases (also included in Table 3).

Key Considerations when Contemplating Deviation from an RCT

Discussion of the case studies, organized along the "development program factors" and their resulting "implications for trial design" (Figure 1), allowed Meeting of the Minds participants to elucidate several key themes that should inform potential deviation from an RCT. This enabled development of a trial-design decision tree (Figure 3), each of the 4 steps of which is discussed in greater detail below. Careful consideration of each step should be undertaken during trial-planning stages and may also prove useful when justifying a particular development plan to regulators and health authorities.

Statistical power

When planning any clinical trial, investigators should perform a statistical power calculation to estimate the likelihood of detecting a clinical effect when one is truly present. Central to power calculations are the expected effect size (i.e., magnitude of expected impact of the experimental intervention) and required sample size. Estimation of the expected effect size relies on a solid understanding of available evidence (e.g., natural disease course, benefit of any effective SOC), and consideration for the minimal effect that would be undoubtedly clinically meaningful for all stakeholders [6]. Importantly, for a given level of statistical power, both the effect size and the time required to show an effect are inversely correlated to the required sample size in an RCT [20]. Hence, the smaller the magnitude of expected treatment effect is compared with SOC or placebo, and the slower it is to manifest, the more patients are required in an RCT to achieve sufficient statistical power.

Table 1
Currently licensed ATMPs (excluding tissue-engineered products), therapy modalities, and treatment indications from both the FDA and EMA.

Brand name	Active substance	Modality	Indication	FDA approval date	FDA trial enrollment (n)	FDA trial design	EMA approval date	EMA trial enrollment (n)	EMA trial design
Abecma[a] (Bristol Myers Squibb, Summit, NJ, USA)	Idecabtagene vicleucel	CAR T cell therapy	Multiple myeloma	March 2021	128	SAT	August 2021	128	SAT
Aucatzyl (Autolus Limited, London, UK, USA)	Obecabtagene autoleucel	CAR T cell therapy	ALL	November 2024	153	SAT	May 2024	153	SAT
Beqvez[a] (Pfizer, New York, NY, USA)	Fidanacogene elaparvovec	GT	Hemophilia B	April 2024	51	SAT	May 2024	51	SAT
Breyanzi (Juno Therapeutics, Inc., Seattle, WA, USA)	Lisocabtagene maraleucel	CAR T cell therapy	BCL	February 2021	286	SAT	April 2022	268	SAT
Carvykti Legend Biotech, Somerset, NJ, USA, and Janssen Biotech, Raritan, NJ, USA)	Ciltacabtagene autoleucel	CAR T cell therapy	Multiple myeloma	February 2022	97	SAT	May 2022	97	SAT
Casgevy (Vertex Pharmaceuticals, Inc., Boston, MA, USA)	Exagamglogene autotemcel	GT	Sickle cell disease	December 2023	44	SAT	February 2024	44	SAT
Elevidys (Sarepta Therapeutics, Cambridge, MA, USA)	Delandistrogene moxeparvovec	GT	DMD	June 2023	54	Blinded RCT	pending	–	–
Hemgenix (CSL Behring LLC, King of Prussia, PA, USA)	Etranacogene dezaparvovec	GT	Hemophilia B	November 2022	54	SAT	February 2023	54	SAT
Imlygic (BioVex Inc., Woburn, MA, USA)	Talimogene laherparepvec	Oncolytic virotherapy	Melanoma	October 2015	436	Blinded RCT	December 2015	419	Blinded RCT
Kymriah (Novartis, Basel, Switzerland)	Tisagenlecleucel	CAR T cell therapy	ALL≤26years, BCL	August 2017	88	SAT	August 2018	68 (ALL), 93 (LBCL)	SAT
Libmeldy[b] (Orchard Therapeutics (Europe) Limited, London, UK)	Atidarsagene autotemcel	GT	MLD	March 2024	10	SAT	December 2020	29	SAT
Luxturna (Spark Therapeutics, Inc., Philadelphia, PA, USA)	Voretigene neparvovec	GT	Retinal dystrophy	December 2017	31	Unblinded RCT	November 2018	31	Unblinded RCT
Lyfgenia (Bluebird Bio, Somerville, MA, USA)	Lovotibeglogene autotemcel	GT	Sickle cell disease	December 2023	35	SAT	April 2024	35	SAT
Roctavian (BioMarin Pharmaceutical, San Rafael, CA, USA)	Valoctocogene roxaparvovec	GT	Hemophilia A	June 2023	134	SAT	August 2022	134	SAT
Skysona (Bluebird Bio)	Elivaldogene autotemcel	GT	CALD	September 2022	32	SAT	July 2021	32	SAT
Strimvelis (GlaxoSmithKline, London, UK)	Autologous CD34⁺ hematopoietic stem cells	GT	ADA-SCID	-	-	-	May 2016	12	SAT
Tecartus (Kite Pharma, Santa Monica, CA, USA)	Brexucabtagene autoleucel	CAR T cell therapy	Mantle cell lymphoma, ALL>26years	July 2020	130	SAT	December 2020	130	SAT

(*continued on next page*)

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Table 1 (*Continued*)

Brand name	Active substance	Modality	Indication	FDA approval date	FDA trial enrollment (n)	FDA trial design	EMA approval date	EMA trial enrollment (n)	EMA trial design
Upstaza[c] (PTC Therapeutics, Warren, NJ, USA)	Eladocagene exuparvovec	GT	AADC deficiency	November 2024	13	SAT	July 2022	13	SAT
Vyjuvek (Krystal Biotech, Inc., Pittsburgh, PA, USA)	Beremagene geperpavec	GT	Epidermolysis bullosa	May 2023	31	Blinded RCT	June 2023	31	Blinded RCT
Yescarta (Kite Pharma)	Axicabtagene ciloleucel	CAR T cell therapy	BCL	October 2017	108	SAT	August 2018	101	SAT
Zevaskyn (Abeona Therapeutics Inc., Cleveland, OH, USA)	Prademagene zamikeracel	GT	Epidermolysis bullosa	April 2025	10	SAT	Pending	–	–
Zolgensma (Novartis)	Onasemnogene abeparvovec	GT	Spinal muscular atrophy	May 2019	15	SAT	May 2020	15	SAT
Zynteglo (Bluebird Bio)	Betibeglogene autotemcel	GT	Beta thalassemia	August 2022	21	SAT	May 2019	23	SAT

Shown are dates and time gaps from the FDA and EMA approvals and the number of included subjects in pivotal trials that formed the basis for positive approval decisions.
AADC, aromatic l-amino acid decarboxylase; ADA-SCID, adenosine deaminase severe combined immunodeficiency syndrome; ALL, acute lymphoblastic leukemia; BCL, B-cell lymphoma; CALD, cerebral adrenoleukodystrophy; CAR T, chimeric antigen receptor T; DMD, Duchenne muscular dystrophy; EMA, European Medicines Agency; FDA, Food and Drug Administration; GT, gene therapy; MLD, metachromatic leukodystrophy; RCT, randomized controlled trial; SAT, single-arm trial.

[a] No longer on the market in the United States or Europe.
[b] Approved in the United States under the brand name Lenmeldy.
[c] Approved in the United States under the brand name Kebilidi.

Table 2
"Meeting of the Minds" participants and affiliations.

Name	Affiliation
Keith Abrams	University of Warwick
Alessandro Aiuti	San Raffaele Telethon Institute for Gene Therapy, IRCCS San Raffaele Hospital
Gunilla Andrew-Nielsen	Swedish Medical Products Agency
Mark Battaglini	ARM
David Bertwistle	Autolus Therapeutics
David Cooper	AviadoBio
Nick Crabb	National Institute for Health and Care Excellence
Julian Delaye	EURORDIS – Rare Diseases Europe
Matt Diver	Galen/Atlantica
Hans-Georg Eichler	Association of Austrian Social Insurances
Dominique Farge-Bancel	Paris University
Miguel Forte	ISCT, Kiji Therapeutics
Nicholas Gertler	Galen/Atlantica
Felix Grignon	ISCT
Niklas Hedberg	Swedish Dental and Pharmaceutical Benefits Agency (TLV)
Jim Lund	ATMP Sweden
Paolo Morgese	ARM
Francis Pang	Orchard Therapeutics
Anne Rosser	Cardiff University
Monica Veldman	ARM
Juan-Jose Ventura	Cancer Patients Europe
Andreas Ziegler	University of Heidelberg

ARM, Alliance for Regenerative Medicine; ISCT, International Society for Cell & Gene Therapy.

With rare diseases, trial-ready patient populations are often exceedingly small due to both the uncommon nature of the condition and the fact that few rare diseases have effective treatment. Inherently, when no effective treatment exists for a condition, patients are less likely to be in regular contact with the healthcare system, making clinical trial enrollment more difficult. *In many rare-disease scenarios, the trial-ready patient population may simply be too small to provide sufficient statistical power for an RCT to detect the true treatment effect. In such cases, an SAT may be justified, especially if the anticipated treatment effect is substantial.*

The pivotal clinical trial of atidarsagene autotemcel (Libmeldy) for the treatment of metachromatic leukodystrophy illustrates this takeaway well (Figure 4) [9]. Here, an SAT was justified based on the small trial-ready patient population alone: being an ultra-rare disease, it took 8 years to enroll only 20 patients. The expected effect size and additional disease and experimental treatment characteristics (e.g., lack of effective SOC, heterogeneity in time to rapid progression and toxicity of the conditioning regimen) also point to choice of an SAT. To provide a basis for comparison, data of patients treated with Libmeldy were compared with an age-matched, untreated natural history cohort.

In the case of Strimvelis, which is authorized in the European Union for patients with adenosine deaminase-deficient severe combined immunodeficiency who are without a matched, related stem-cell donor, the case for an SAT based on population size alone appears similarly strong: only 1:200,000 to 1:1,000,000 infants are born with the monogenic disease (~10-15 total per year in the European Union) [10]. Additional factors (e.g., large expected effect size, lack of viable treatment alternative, limited possibility of crossover, treatment burden or difficulty of blinding due to required autologous stem cell collection, and unethical randomization to treatment with expected higher morbidity and mortality) also support the choice of an SAT.

Effect size and enrollable patient population can interact in interesting ways:

- ☐ As discussed above, the case of a large effect size and small patient population suggests use of an SAT.
- ☐ In an extreme version of this scenario, effect size can be so dramatic that even a handful of patients could, *in theory,* power an

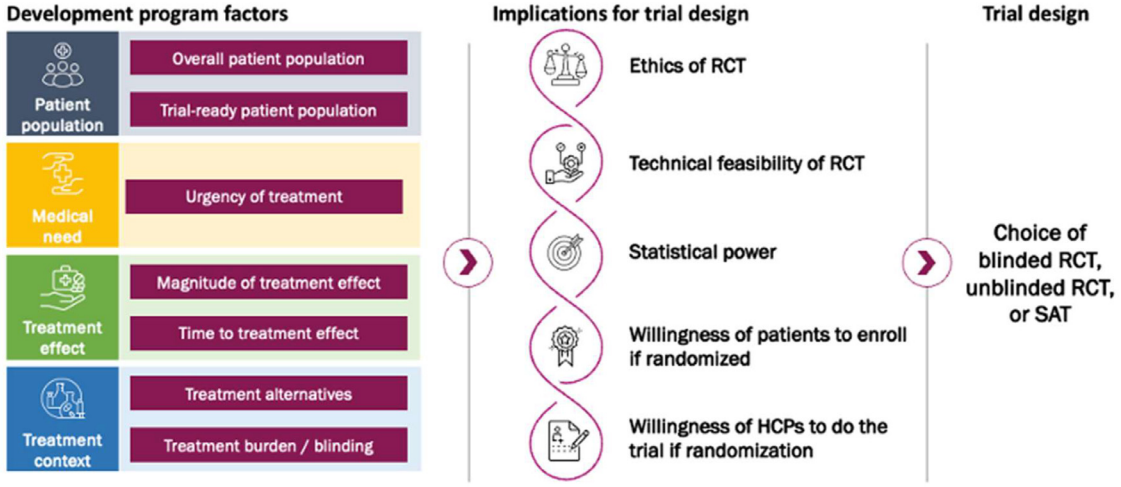

Fig. 1. Development program factors and their implications for choosing a trial design [7,14–19]. Each of the seven factors shown on the left has distinct, yet often overlapping, impact on the ethics, practicality and robustness of an RCT. HCP, healthcare provider. (Color version of figure is available online.)

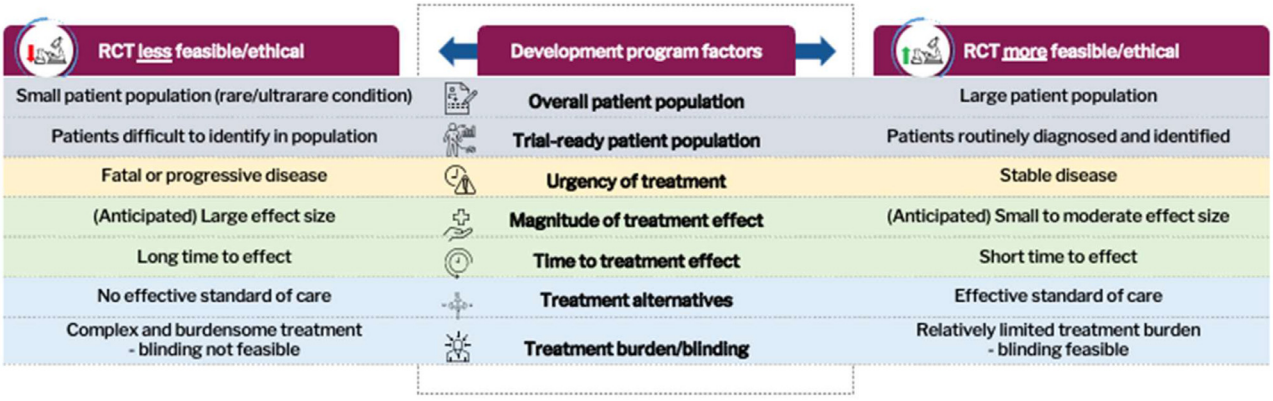

Fig. 2. Further breakdown of the key development program factors. Each of the seven factors (shown in the middle column) can present in a way that makes RCTs less feasible or ethical (left column) or more feasible or ethical (right column). (Color version of figure is available online.)

Table 3
Rare-disease targets and treatment modalities covered by case studies.

Rare-disease target	Treatment	Modality	Conditioning regimens and/or administration requirements
Huntington disease	(Early-stage)	*In vivo* intrastriatal AAV gene therapy delivered under MRI guidance	12- to 14-hr brain surgery
Frontotemporal dementia	(Early-stage)	In vivo intrathalamic AAV gene therapy delivered under MRI guidance	8- to 10-hr brain surgery
Metachromatic leukodystrophy	Atidarsagene autotemcel (Libmeldy, Orchard Therapeutics (Europe) Limited, London, UK)	Genetically modified hematopoietic stem cells, ex vivo	Bone marrow ablation
Relapsed refractory adult B-cell acute lymphoblastic leukemia	Obecabtagene autoleucel[a]	Autologous CAR T cells, *ex-vivo*	Immune system ablation
Adenosine deaminase-deficient severe combined immunodeficiency	Strimvelis (GlaxoSmithKline, London, UK)	Autologous ex-vivo gene-modified bone marrow replacement	Low-dose busulfan
Systemic sclerosis	(Early stage)	Autologous hematopoietic stem cell transplantation[b]	Immune system ablation
Duchenne muscular dystrophy[c]	Delandistrogene moxeparvovec[d]	Recombinant AAV-based gene therapy delivered IV	Corticosteroids
Inherited retinal dystrophy[c]	Voretigene neparvovec (Luxturna, Spark Therapeutics, Inc., Philadelphia, PA, USA)	Recombinant AAV-based gene therapy injected subretinally	Corticosteroids, subretinal injection

AAV, adenovirus-associated vector; ATMP, advanced therapy medicinal product; CAR, chimeric antigen receptor; IV, intravenously; MAA, marketing authorization application; MRI, magnetic resonance imaging.
[a] MAA under review by the EMA; approved in the United States as Aucatzyl®.
[b] Not an ATMP, but illustrative of factors influencing trial design for rare conditions.
[c] Not discussed during the meeting but explored later in the paper as examples of specific study designs.
[d] MAA under review by the EMA; approved in the United States as Elevidys®.

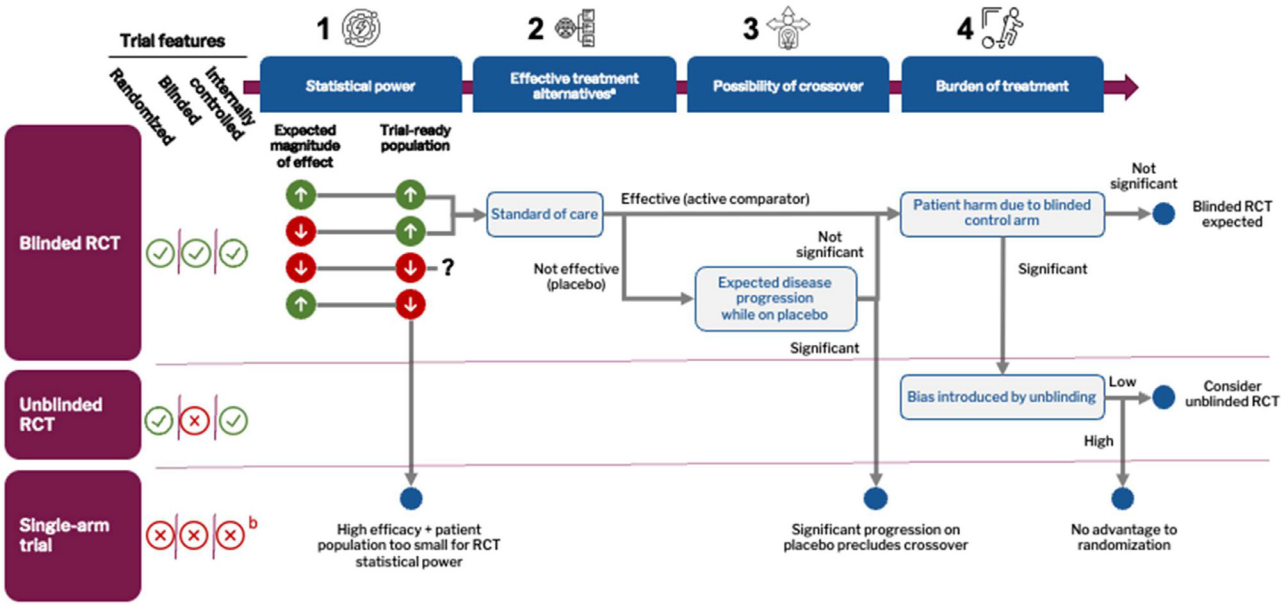

Fig. 3. "Decision tree" of considerations driving potential deviation from RCT standard. This flowchart should be approached in a step-wise fashion to determine whether a blinded RCT, unblinded RCT or an SAT is appropriate. [a]Symptomatic treatments have clear role to play but, as comparators, may obscure the impact of disease-modifying therapies when trial duration is short. [b]Trial lacks built-in control but can be supplemented with external controls. (Color version of figure is available online.)

RCT effectively. In such cases, however, clinical equipoise would be difficult to maintain. Here, an SAT may be the only ethical option.

- ☐ Another scenario in which both the magnitude of expected effect and enrollable patient population are exceedingly small presents a conundrum. In such cases, an RCT will be underpowered, and an SAT will also struggle to show clinically meaningful benefit. One could argue that investigation of any potential rare-disease therapy under those conditions lacks both clinical merit and eventual commercial feasibility.
- ☐ Finally, in cases where the enrollable patient population is large, this factor alone does not justify deviation from the (blinded or unblinded) RCT standard.

Effective treatment alternatives

When an effective SOC exists for a given disease, the assumption should be to conduct a blinded RCT (although, as discussed below, other factors may still suggest either an unblinded RCT or an SAT). Unfortunately, effective therapy or therapies exist for very few rare diseases and, although symptomatic treatments have a clear role to play, their use as 'active' controls may obscure the impact of truly disease-modifying therapies, particularly in situations when the trial duration is short in comparison to the natural evolution of the disease. As such, when considering experimental designs for rare-disease therapies, placebo is often the only practical comparator.

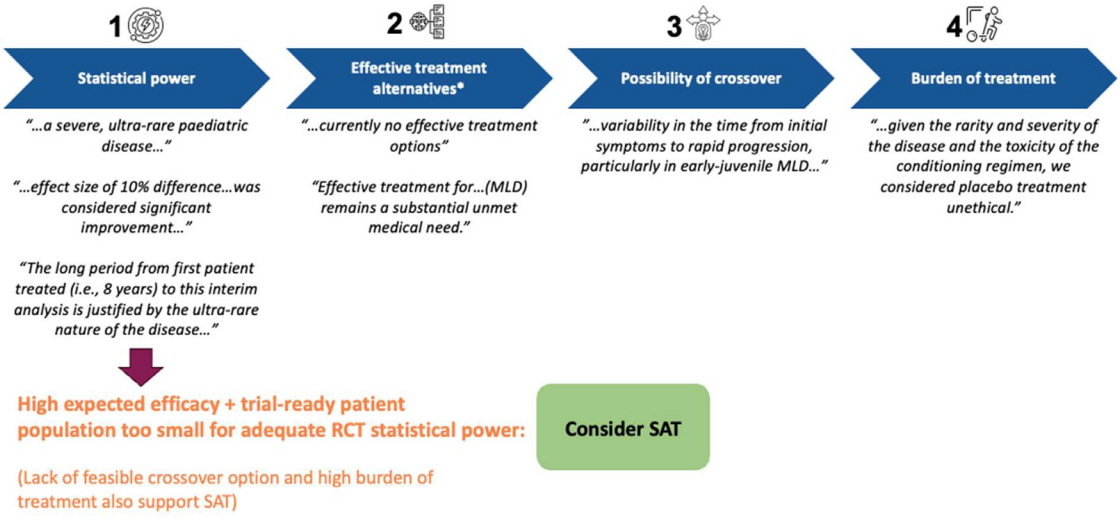

Fig. 4. Features of the SAT along the development program factors that contributed to approval of Libmeldy in the European Union [9]. Despite the high expected magnitude of effect, the exceedingly small trial-ready patient population would prohibit adequate statistical power in an RCT. This, alone, likely justifies choice of an SAT. Further justification for an SAT is provided by the impossibility of crossover (due to the rapid progressive nature of the disease) and the burden of mimicking the experimental treatment (involving a myeloablative conditioning regimen) in a placebo arm. (Color version of figure is available online.)

Possibility of crossover to alleviate the impact of allocation to placebo

When allocation to placebo is being considered, the clinical trial designer must balance the desire for useful information about the efficacy of the experimental treatment with the imperative to avoid harm to clinical trial enrollees. The possibility of crossover can preserve this balance if patients assigned to placebo can still benefit from the experimental treatment at the time of prespecified crossover (and if the trial establishes the treatment's positive benefit-risk balance). Ultimately, crossover can serve patients assigned to placebo when the therapeutic window is long relative to the time required to observe the experimental treatment effect. For example, if patients have a 3- to 5-year treatment window after systemic sclerosis diagnosis and an experimental treatment is expected to manifest its effect in 1 to 2 years, there may be adequate time for patients in a placebo arm to crossover to the experimental arm.

However, scenarios involving rapid (and particularly irreversible) disease progression relative to the time required to observe an experimental treatment effect can make crossover of little or no value to patients. In such situations, initial allocation to placebo condemns patients to worsening of their disease, or even death, thus compromising the ethics of an RCT when a potentially beneficial experimental treatment is available in the trial. This scenario is illustrated well by the case of frontotemporal dementia, where rapid clinical progression, aphasia and brain atrophy occur within 1-2 years of symptom onset and time to observe an experimental treatment effect may be up to 24 months. In this scenario, a significant proportion of patients could suffer irreversible brain atrophy while on placebo and be unable to complete the assessments required to determine crossover eligibility.

Inherently, when crossover is allowed in trials of diseases with rapid and irreversible progression, it may have to occur so early that even a true difference between the outcomes in the experimental and the control arm cannot be detected. In such cases, the point of conducting the trial becomes moot. In addition, even where the treatment window would allow for crossover, the movement of patients from, for example, placebo to active arms can cause inferential issues in estimated endpoints such as overall survival. Methods to overcome such bias rely on additional assumptions and data requirements [21].

Hence, although crossover is often viewed as a "safety mechanism" or "escape" built into an RCT, it is not always a feasible way to make a control group viable, and its timing and practicality are crucial considerations. Successful crossover designs rely on a solid understanding of the natural disease course (including rapidity of symptom onset and the reversible and irreversible nature of those symptoms) and informed expectations of time-to-effect for the experimental treatment.

Combining the considerations for crossover with takeaways from the "*Effective treatment alternatives*" section: *In cases where there is no effective SOC and the possibility of crossover is not sufficient to prevent patients randomized to a placebo arm from experiencing significant disease progression during the trial, an SAT may be warranted*.

Burden of treatment and feasibility of blinding

When comparing two treatment arms, the act of blinding conveys inherent bias-reducing features that maximize the internal validity of the study. Blinding of study participants protects against bias introduced by treatment expectations or differential adherence to the trial protocol, whereas blinding of study personnel (e.g., physicians, evaluators) reduces the risk of differential patient management (other than allocation to experimental or control treatment, e.g., addition of symptomatic treatments) or assessment bias [5]. Provided other disease-, treatment- and patient-related factors are amenable to an RCT design, blinding (ideally full blinding—patients, physicians and all other study personnel masked to treatment assignment) should be pursued when feasible.

Notably, the complex and burdensome treatment required for many ATMPs can make a blinded control group technically and ethically challenging. This was illustrated well by case studies of Huntington disease and frontotemporal dementia treatment delivered directly to the brain, where sham neurosurgery would be required in a blinded placebo group. Such an approach has obvious implications for patients, surgeons and treatment centers, and may also be deemed unethical by regulators and institutional review boards. Similarly, in the case of a chimeric antigen receptor T cell therapy for relapsed or refractory adult B-cell acute lymphoblastic leukemia, putting a patient through leukapheresis, possible bridging therapy, and lymphodepleting chemotherapy to ultimately give them placebo would be ethically questionable. At the same time, offering an active comparator (e.g., SOC chemotherapy or monoclonal antibody) in a relapsed or refractory population could leave some patients receiving therapy they have already progressed on (also ethically questionable).

Conversely, the example of delandistrogene moxeparvovec-rokl illustrates a case where blinding is more feasible and ethical. In the blinded, crossover RCT (Figure 5) that contributed to its US approval [22], a blinded placebo arm appears rational because of the treatment's single intravenous administration and lack of complex preconditioning regimen (corticosteroids only).

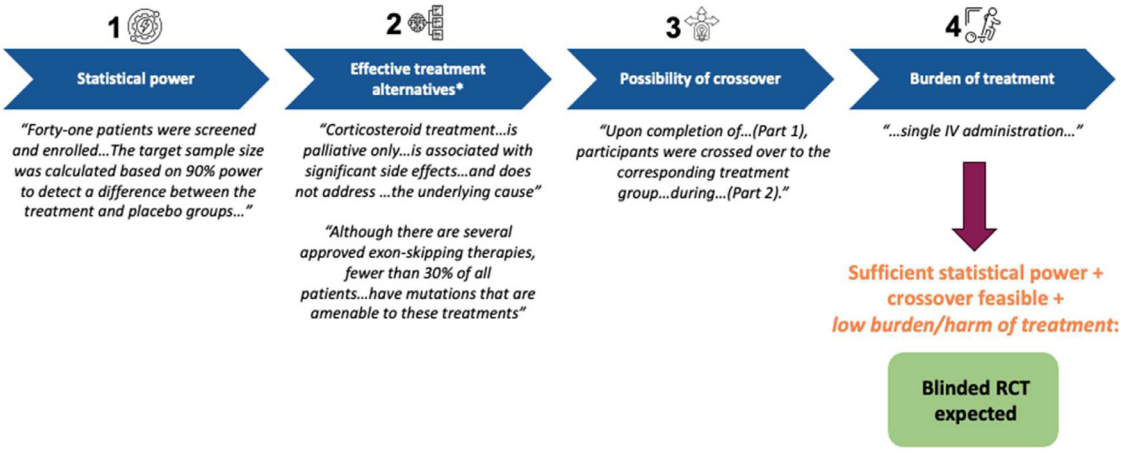

Fig. 5. Features of a blinded RCT that contributed to the approval of Elevidys, (Sarepta Therapeutics, Cambridge, MA, USA) in the United States, and review, at the time of this writing, by EMA [22]. In this case, statistical power was adequate for an RCT, crossover to placebo (no effective SOC) was possible and the single IV administration was considered of low enough burden to patients that blinded randomization was possible. Data from two SATs also supported the initial US approval [23–25], and a second blinded, placebo-controlled RCT (NCT05096221) led to expanded approval in the United States (to all patients > 4 years of age) [26]. All available evidence is currently under review by the EMA. (Color version of figure is available online.)

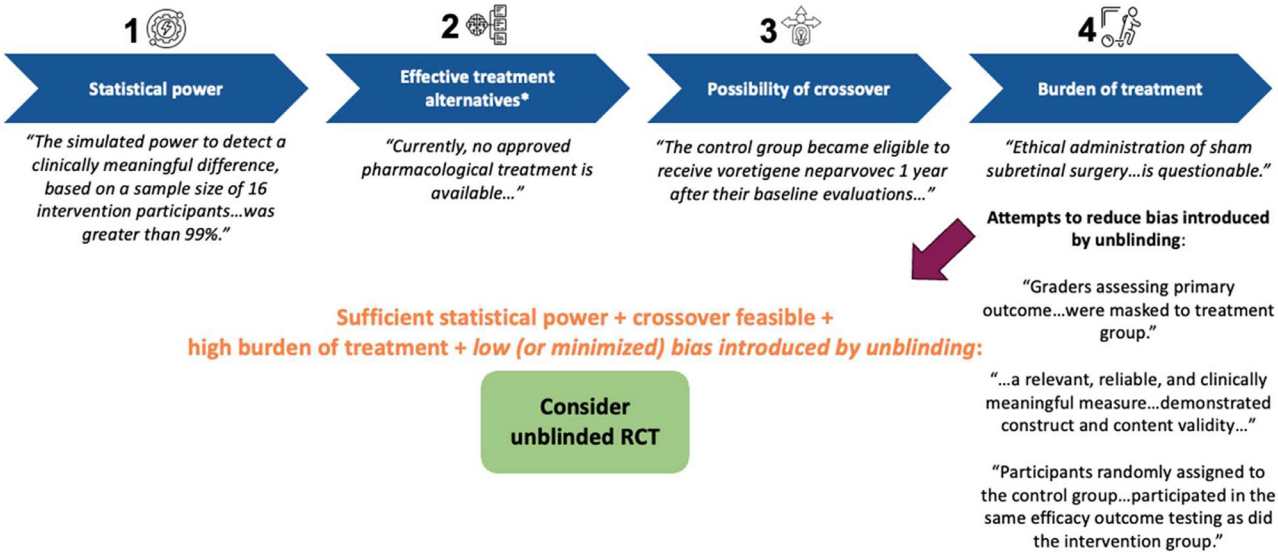

Fig. 6. Features of the unblinded RCT that led to approval of Luxturna [29]. In this case, statistical power was sufficient to support an RCT, crossover to placebo (no effective SOC) was possible and, because significant attempts were made to reduce bias introduced by unblinding the patients and treating physicians, an unblinded RCT was deemed feasible. (Color version of figure is available online.)

Deviation from the RCT standard should be considered where imposing the full burden of the experimental treatment on the control arm is not justifiable. An RCT can be conducted without blinding all participants and researchers to the treatment being received. Unblinded (or "open-label") RCTs may be warranted in specific situations, including those where the intervention is highly recognizable because of its dramatic physiologic effects or when treatment-induced adverse events are likely [27,28]. In situations where full blinding is impractical, bias can be minimized by blinding as many people associated with the trial as possible [11]. Non-participant or non–treating-physician candidates for blinding include data collectors, central independent adjudication committees, outcome assessors and statisticians [11]. Accordingly, blinding should be viewed as a continuum rather than as an all-or-nothing aspect of trial design [5]

Choice of endpoint(s) becomes particularly critical when any level of blinding is eliminated. The resulting risk of bias is greatest with respect to subjective endpoints, and potentially less significant with regard to objective measures [5,11], although bias can still be introduced into objective endpoints through differing patient management practices (e.g., frequency of follow-up, treatment of complications). Importantly, any surrogate outcomes used as trial endpoints should be fully validated and, regardless of endpoint choice, outcomes should be collected identically for both arms of the trial [11]. Considerations for partial blinding, choice of clinical trial endpoint(s) and endpoint measurement are illustrated well by design of the pivotal phase 3 trial of voretigine neparvovec (Luxturna, Spark Therapeutics, Inc., Philadelphia, PA, USA) for RPE65-mediated inherited retinal dystrophy (Figure 6) [29].

When assignment to a randomized, blinded control arm could impart an unethical burden or patient harm, the trial may be unblinded while retaining randomization. At this point the degree of bias introduced by such unblinding should be examined. When unblinding introduces such extensive bias that it seriously clouds the ability to attribute the outcome to the intervention, then the point of randomization likely becomes moot. In such cases, an SAT may be warranted. This is illustrated well by the case of an experimental gene therapy for Huntington disease or frontotemporal dementia, where unblinding the patient or treating physician to avoid a medically unnecessary "sham" brain surgery could introduce such significant bias that the benefits of randomization are negated. Patients and caregivers may be less committed to the trial (and even drop out), whereas it may be impossible for physicians to treat a patient who has undergone brain surgery identically to one who has not.

Filling Gaps in Comparative Data when SATs Are Used

As highlighted in the EMA's recent reflection paper on SATs [12], "the design does not support an inherent [internal] causal interpretation as an effect of the investigational treatment and must rely on knowledge external to the SAT about the outcomes of subjects that would be observed had they not been treated with the investigational treatment." Hence, when SAT designs are used for pivotal studies, external knowledge is essential for drawing meaningful comparisons and justifying causality.

Meeting participants briefly reflected on methodologies and sources for external knowledge, including data from natural history studies, high-quality registries and treatment and placebo arms of prior clinical trials (i.e., synthetic controls). Though not the primary focus of the meeting and discussed in both the literature and regulatory documents [14,18,30–32], important takeaways emerged from group discussion.

First, proactive planning of an external comparator is essential. This could take the form of natural history studies performed concurrently with (or prior to) pivotal SAT execution, or the creation and funding of disease registries that use similar inclusion and exclusion criteria and endpoints to the SAT.

Second, the existence of multiple registries for a single disease and the general lack of data harmonization (e.g., types of collected data, measurement techniques) across those registries is problematic for generating usable external comparators for SATs. This was regarded as an important area of opportunity for the ATMP community, and one worthy of further exploration and multi-stakeholder investment.

Conclusion

This Meeting of the Minds convened stakeholders from across the ATMP ecosystem to clarify appropriate means for investigating rare-disease therapies. Through the discussion of several ATMP development case studies embedded in a structured framework that is also applicable to future development programs, participants laid out a step-by-step set of considerations to guide the choice of trial design. This trial-design decision tree can guide investigators, regulators and HTA bodies through the rationale behind an approach to data generation. By stepwise examination of inputs for statistical power calculations, alternative treatment options, feasibility of crossover designs

and burden of therapy and impact of blinding, decision-makers can assess whether deviation from the blinded RCT gold standard is warranted. In cases where SATs are the only feasible and ethical option, efforts must be made to draw robust comparisons between the study group and external controls that arise from high-quality sources.

As illustrated in the decision tree, three development scenarios stood out as justifying deviation from the RCT standard:

- ☐ Cases where the experimental treatment is expected to have high efficacy but the enrollable patient population is too small to support an RCT with the requisite statistical power.
- ☐ Cases where there is no effective SOC and the possibility of crossover is not sufficient to prevent patients randomized to a placebo arm from experiencing significant disease progression during the trial.
- ☐ Cases where the patient burden of treatment (such as chemotherapy to ablate the immune system in chimeric antigen receptor T cell therapy or brain surgery to deliver an experimental agent to the central nervous system) is sufficiently severe to raise ethical concerns about exposing patients randomized to a control arm to the same protocol. Note that this scenario suggests unblinding the trial—but raises the question of whether the potential bias introduced by unblinding introduces too much bias to make an RCT worthwhile—or suggests proceeding with an SAT.

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