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Review Article

Alpha-1 Antitrypsin Deficiency (AATD): Navigating the Drug-Development Pathway to Successful Clinical Trial Execution

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Abstract

Alpha-1 antitrypsin deficiency (AATD) is a rare genetic condition with heterogeneous, genotype-dependent lung and liver manifestations. In the lungs, insufficient levels of the alpha-1 antitrypsin (AAT) protein result in elastase-driven elastin destruction ('toxic loss of function'), driving chronic inflammation and causing chronic obstructive pulmonary disease (COPD), emphysema and bronchiectasis [1]. In the liver, pathologic AAT polymerisation causes hepatocellular accumulation ('toxic gain of function'), leading to neonatal hepatitis, cirrhosis and hepatocellular carcinoma [2].

The patient journey to diagnosis and treatment is usually challenging and brings a significant burden to patients and their families. Current treatment alternatives are also suboptimal and fail to completely halt disease progression, resulting in an unmet medical need. The development of new treatment options that reduce patient burden, stop disease progression and improve quality of life is, therefore, vital.

Successful clinical trials require an end-to-end clinical development plan that anticipates regulatory expectations across regions, builds a robust safety database early and incorporates efficacy endpoints that can withstand scrutiny from regulatory agencies and brings it inside the study protocol design. Equally, successful execution depends on early and sustained patient involvement, realistic country-site strategies grounded in population availability and care pathways, and a focus on enrolment, retention and endpoint protection without imposing excessive burdens on participants and sites.

Drawing primarily on first-hand experiences of developing operational plans for AATD studies, this article outlines critical considerations for sponsors navigating the AATD clinical development pathway, including protocol design choices for early-phase and pivotal studies. The article also offers practical guidance on trial execution in this rare disease setting, including how to identify the country-site mix; the value of patient advisory boards (PABs), key opinion leaders (KOLs) and referral networks in enrolment; and how decentralised components can mitigate patient burdens to improve retention.

Keywords: *Alpha-1 Antitrypsin Deficiency; Alpha-1 Antitrypsin; Rare Diseases; Genetic Disorders; Pulmonology; Hepatology; Augmentation Therapy; Clinical Trials; Clinical Development; Decentralised Trials; Patient Advisory Boards; Key Opinion Leaders; Investigative Sites*

Abbreviations

AAT: Alpha-1 Antitrypsin; AATD: Alpha-1 Antitrypsin Deficiency; AIR: Alpha One International Registry; APAC: Asia-Pacific; COPD: Chronic Obstructive Pulmonary Disease; EARCO: European Alpha-1 Research Collaboration; EMA: European Medicines Agency; FDA: Food and Drug Administration (US); ICH: International Council for Harmonisation; IDW: Inverse Distance Weighted; KOL: Key Opinion Leader; MAA: Marketing Authorisation Application; MHRA: Medicines and Healthcare Products Regulatory Agency (UK); OLE: Open Label Extension; PAB: Patient Advisory Board; PIP: Paediatric Investigation Plan; RNA: Ribonucleic Acid

Introduction

Designing and delivering clinical trials in AATD must begin with the lived reality of patients. Many individuals reach diagnosis only after years of non-specific symptoms and fragmented care [3]. When considering research participation, these patients must also balance work, family responsibilities and travel burdens, as research facilities may lie far away from their residence.

Against this backdrop, sponsors face the central tension of rare-disease research: the need to generate robust, decision-enabling evidence in small, heterogeneous populations that are scattered across wide geographies (See figure 1). This tension is amplified by cross-regional differences in testing rates, genotype distributions, infusion infrastructure and access to augmentation therapy, all of which influence where patients are diagnosed, how they are managed and whether they can realistically take part in research.

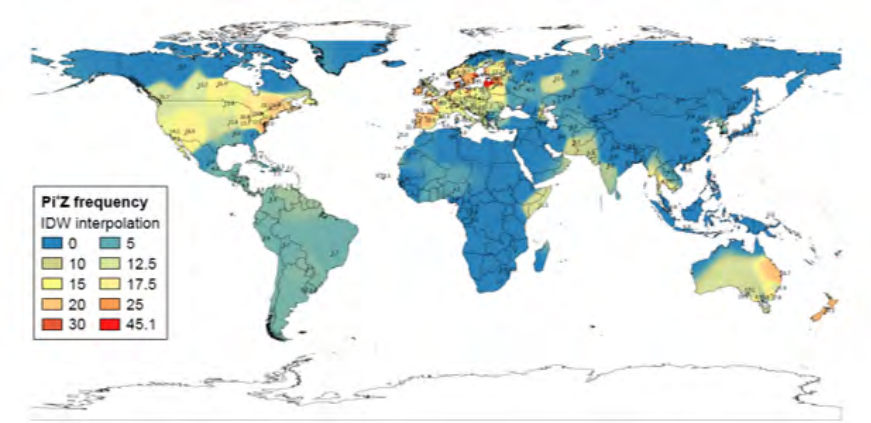

Figure 1: *Global distribution of AATD patients with Pi*Z genotype (x1,000), estimated using inverse distance weighting (IDW) interpolation [4].*

From a clinical development perspective, the question is, therefore, not only how to design a scientifically rigorous trial, but how to ensure that participation meaningfully contributes to patient treatment and wellbeing. Trials in AATD should be conceived as an extension of care, offering access to potential new therapies and structured follow-up while avoiding unnecessary burdens in visit schedules, procedures and travel. Achieving this balance requires foresight on endpoints and safety requirements, flexible operational models and sustained engagement with patients, clinicians and advocacy networks.

In what follows, we adopt a pragmatic, patient-centred lens: what must sponsors build into a clinical development plan from day one so that trials are both feasible for patients and credible for regulators. How can they execute trials so that they support day-to-day care, enhance treatment options and protect scientific integrity - without imposing disproportionate burden on participants and their families?

Designing and conducting successful clinical trials in AATD

In AATD clinical development, operational priorities are strikingly consistent across programmes and sponsors. Study designs must minimise patient burden while preserving the integrity of endpoint windows and the precision of outcome measures; recruitment strategies must extend beyond traditional site database screening to reliably reach an already rare, frequently underdiagnosed population; and operational execution must apply proportionate, risk-based quality oversight to maintain control of both systematic and random error. When executed well, these practices underpin predictable screening velocity, durable patient retention and stable, interpretable datasets from first-patient-in through database lock.

Translating these priorities into operational reality requires discipline in both recruitment strategy and protocol design.

The first principle is that default site database screening alone will almost always under-deliver - reflecting low disease awareness, heterogeneous diagnostic practices and geographically diffused patient populations. Sponsors must, therefore, establish referral channels that intentionally reach beyond the walls of specialist centres. These include registry partnerships (where available), digital outreach campaigns targeting at-risk individuals and structured community physician referral pathways that link non-specialist clinicians to participating centres.

The second principle is the radical simplification of protocol and schedule design, focusing on elements that are operationally essential rather than academically desirable. Each additional assessment, visit or procedure introduces friction for patients who are often managing chronic respiratory, hepatic or multisystem disease. Reducing this burden through visit consolidation, flexible scheduling, travel support and decentralised options has a significant impact in AATD, where attending specialist centres may involve long distances or cross-regional referral. Guidance indicates that appropriately governed decentralised components - such as local laboratory testing, telemedicine for non-complex assessments and home health visits for non-dosing procedures - can materially expand access, reduce patient fatigue and improve retention without compromising endpoint integrity [5].

Together, these principles support an operational model tuned to the practical realities of AATD: a rare, variably diagnosed condition requiring proactive outreach and low-burden engagement strategies to assemble and maintain a representative study population. When executed with discipline, this model supports stable enrolment trajectories, high completion rates and endpoint datasets with reduced noise - ultimately, increasing the probability of conclusive trial outcomes for a population that urgently needs new therapeutic options.

Key strategic considerations for study development and execution

A successful AATD programme is built long before first-patient-in. Key decisions during the early design stages - what evidence to generate, how to generate it, where patients can be enrolled and who enables reach - define the study development plan and shape a coherent strategy to protect endpoints. Equally, the way these decisions are operationalised across sites, systems and workflows determines the quality and consistency of trial execution. Together, these choices shape every downstream detail to optimise feasibility, scientific credibility and patient experience from day one, and then sustain these standards throughout the full duration of the study.

Early inclusion of efficacy endpoints and safety requirements

The ICH E6(R3) framework underscores proportional, risk-based quality management and supports trial designs that integrate modern technologies and decentralised elements where appropriate [6].

AATD programmes must orchestrate early-phase studies that characterise pharmacokinetics and safety but also set up credible signals for later phases. As a result, sponsors should map which biomarkers (for example, total serum AAT levels or mechanistic markers aligned

to the product class) and which clinical measures are sufficiently reliable and interpretable within small samples before planning an interim analysis that informs go/no-go decisions without over-promising.

Equally, the size and composition of the safety database required for marketing applications should be estimated up front, with strategic use of open-label extensions and pooled analyses across phases to reach thresholds that agencies typically expect and have agreed upon for the specific project. For instance, while a paediatric investigation plan (PIP) is often waived for augmentation therapy targeting lung involvement, newer modalities such as RNA-editing therapies usually require a comprehensive PIP. In practice, this is likely to generate a second, distinct line of investigational development because these approaches address a different disease phenotype that predominantly affects the liver rather than the lungs.

In operational terms, these decisions about endpoints and safety should drive early setup of critical systems and central readers. For lung-function and imaging endpoints, this typically means establishing central spirometry and imaging core laboratories with standardised acquisition protocols, training and quality checks, alongside any blinded endpoint adjudication committees that may become required. Safety oversight should be supported by robust pharmacovigilance systems, predefined data-review cycles and near real-time detection of safety signals, integrated with the electronic data capture and central monitoring platforms used to manage study data across sites.

Anticipating divergent regional expectations

Sponsors developing AATD therapies rarely aim for a single jurisdiction; most intend to seek marketing authorisation across multiple regions. Differences in methodological and regulatory interpretations can, therefore, emerge around endpoint hierarchy, biomarker validation, required duration of follow-up and the acceptability of external-control evidence - an approach sometimes considered in rare disease programmes.

To pre-empt this divergence, sponsors should plan parallel scientific advice with key agencies, such as the European Medicines Agency (EMA), US Food and Drug Administration (FDA), the UK Medicines and Healthcare products Regulatory Agency (MHRA) and Health Canada, using these consultations to harmonise the clinical development plan with multi-region marketing authorisation application (MAA) objectives.

For example, when clinical endpoints like forced expiratory volume decline or liver fibrosis progression require long follow-up, developing an early strategy for intermediate or surrogate markers - such as elastography-based liver stiffness, quantitative computed tomography densitometry or validated serum biomarkers - can help de-risk regulatory discussions. Where appropriate, sponsors may also map these markers against long-term clinical outcomes using modelling and simulation to strengthen justification for their use. Similarly, if the target population includes individuals with rapidly progressive liver disease, proactively defining expanded access or compassionate use frameworks ensures consistent access pathways that do not compromise trial integrity or the evidentiary package. In programmes incorporating external or hybrid control arms, early consultation with regulators can clarify requirements around data provenance, statistical adjustment methods and robustness thresholds.

Taken together, these early and coordinated regulatory interactions help convert heterogeneous expectations into a coherent, globally defensible study design and development programme - one capable of supporting integrated and synchronised submissions across regions.

Understanding the competitive landscape

Industry analysis indicates that multiple AATD trials are expected to recruit across the next planning horizon, with activity heavily focused on early-phase clinical studies (See table 1) and centred in North America and Europe (See table 2). Sponsors should, therefore, assume that site and patient attention will be contested.

Trial Phase	No. of Clinical Trials
Phase III	6
Phase I/II	5
Phase II	4
Phase I	2
Phase IV	1

Table 1: *Number of AATD clinical trials potentially recruiting in 2026 by study phase [7].*

Geographic Region	No. of Clinical Trials
North America	14
Europe	11
APAC	8
South America	3

Table 2: *Number of AATD clinical trials potentially recruiting in 2026 by geography [7].*

In such competitive contexts, drug development programmes with patient-centred schedules, reliable logistics support and transparent communications tend to secure earlier commitments from both sites and participants.

A three-part, concurrent approach is recommended here to de-risk feasibility and accelerate compliant enrolment across jurisdictions. In practice, these workstreams progress in parallel - sometimes staggered for sequencing efficiency, but never as a linear chain. Sponsors should activate experienced centres early and maintain close engagement; coordinate with registries to identify pre-screening pools in a compliant manner; and deploy targeted, centrally managed digital outreach with clear routing to site-level screening teams, ensuring content meets non-promotion standards in each jurisdiction.

Identifying the country-site mix and geo-targeting

Country and site selection should be grounded in where patients are available, starting from prevalence and genotype distribution data and then modulating this by standard of care (including disease-modifying intravenous augmentation therapy), reimbursement status, the number of experienced sites in each country, previous performance of those sites, regulatory strategy, site capabilities and the local regulatory framework (including time to country activation). As such, country selection cannot be divorced from testing practices, reimbursement realities and site experience with AATD phenotyping, lung-function testing and infusion services.

The availability of augmentation therapy also has important implications for eligibility and patient motivation. Where augmentation therapy is routinely reimbursed (and specialist centres are active), testing and referral may be more proactive, creating a larger pool of diagnosed candidates; elsewhere, patients may be underdiagnosed or concentrated in a few referral hubs, affecting both reach and equity. However, in many AATD trials, patients receiving augmentation are excluded or would need to interrupt treatment before enrolment. These individuals may be, understandably, reluctant to stop a therapy they perceive as beneficial, even if its impact on disease progression is imperfect. In practice, when the goal is to maximise enrolment, sponsors often prioritise countries where augmentation therapy is not reimbursed or only partially available, and where both patients and sites are more eager to participate in studies that offer access to investigational treatments and structured follow-up.

Geo-targeting then refines this high-level country mix by identifying where eligible patients are most likely to be found within and across countries. This can involve the use of health-claims data or tokenised electronic health records to locate clusters of patients with

relevant diagnostic codes, spirometry patterns or referral histories, complemented by insights from registries and specialist networks. Geo-targeting may also mean deliberately selecting countries or regions with specific characteristics of interest for the product or population - such as particular patterns of healthcare utilisation, genotype distribution or environmental exposures.

A neutral geography strategy that blends North America, Europe and selected additional regions (such as Australia) often proves highly resilient - provided eligibility criteria and visit logistics are calibrated so that patients outside major urban centres are not inadvertently excluded. While this approach typically increases total study costs, those costs can be offset by the operational advantages it delivers, such as broader patient access, more predictable screening velocity and reduced dependence on any single regulatory or healthcare system. These gains frequently translate into shorter overall study timelines, enabling sponsors to finalise pivotal datasets sooner and advance MAAs in parallel across regions. In turn, earlier MAAs can accelerate commercial entry, helping to balance and, in some cases, surpass the incremental investment required to run a globally distributed programme.

By distributing recruitment and regulatory engagement across jurisdictions, sponsors maintain a fair, realistic opportunity for participation while simultaneously safeguarding timeline resilience.

Patient enrolment strategies

Enrolment in AATD trials rarely succeeds through a single channel. Instead, sponsors need a coordinated strategy that combines local databases and registries, trusted referral networks and advocacy partners, and carefully governed public-facing campaigns to convert a small, dispersed pool of eligible patients into a steady flow of screened and enrolled participants.

Local databases and registries

Site databases at experienced centres are often the fastest way to generate early screenings, particularly where coordinators maintain up-to-date rosters of genotyped adults and have embedded spirometry capacity. However, database mining alone rarely sustains enrolment beyond the initial surge. Sponsors should, therefore, pair database pulls with simple referral tools for non-investigator clinicians and schedule frequent touchpoints with coordinators to refresh lists, reconcile pre-screen failures and adjust feasibility assumptions.

Registries can extend reach beyond individual centre catchment areas. The Alpha One International Registry (AIR) provides a multinational framework through which many countries contribute phenotype and clinical data; its long-standing infrastructure and cross-border network have enabled large observational datasets [8]. The European Alpha-1 Research Collaboration (EARCO) operates a prospective pan-European AATD registry open to investigators and expanding beyond Europe; it explicitly supports longitudinal, real-world data collection useful for feasibility planning [9]. Sponsors should seek early, compliant engagement with registry owners to clarify permissible contact methods and to coordinate with principal investigators at participating sites.

Patient and advocacy engagement as enrolment drivers

Patients frequently report that they prefer to hear about trials from their specialist [10]. Yet, many AATD patients are not followed at the specific sites participating in a given study. Referral networks, PABs and advocacy groups thus function as connective tissue - signposting interested people to screening sites and helping clinicians unfamiliar with trial processes to refer appropriately.

When PABs are convened before finalising the schedule of assessments, patient feedback often leads to tangible protocol design improvements, such as clearer consent language and fewer duplicative procedures. Additionally, experience across AATD planning demonstrates that PABs surface avoidable burdens hidden in otherwise ‘standard’ schedules, such as clustering spirometry, imaging and blood draws on the same day for patients who fatigue easily or extended recovery time after pulmonary-function testing before other assessments. In this way, early patient input directly shapes completion of the study design so that it addresses key scientific questions without imposing unnecessary burden.

Patient-engagement frameworks echo these benefits, highlighting that PABs offer unmatched insight into improving study feasibility, recruitment and retention, while revealing patient views and openness to existing methods, emerging practices and technology-enabled solutions [11]. Beyond protocol design, PABs and advocacy partners can amplify awareness and explain trial purpose, eligibility basics and participation logistics without promoting any investigational product.

However, it is also important to emphasise that patient organisations and advocacy groups are not recruitment channels and should never be approached as mechanisms to 'find patients' or pre-screen potential subjects. Their mission is to improve patients' lives, reduce burden, promote dignity and support access to effective treatment - a goal fully aligned with ethical research practice.

When sponsors and clinical research organisations engage with these organisations, the relationship must be built on mutual respect, transparency and inclusion, not transactional expectations. From the outset, sponsors should make clear that patient organisations have a meaningful voice in shaping the study, including providing input into protocol design, feasibility considerations, burden reduction strategies and communication plans. These patient groups must be respected as partners, not observers. Equally, they should be assured that their community members will be informed promptly and respectfully if a study is paused, amended, interrupted or cancelled, along with an explanation of the steps taken to protect participants and uphold their rights.

Approached this way, collaborations with patient organisations help ensure the trial is acceptable, accessible and ethically grounded. Advocacy groups may choose to welcome the study, share balanced information with their members or encourage participation without promoting the trial because they understand how the study aligns with patient priorities and safeguards their well-being. This partnership mindset helps counter perceptions that the industry views patients merely as 'subjects for testing' and instead reinforces that they are co-developers of better research and outcomes.

KOLs, investigative sites and referral networks

Alongside PABs, early involvement of KOLs and prospective investigative sites at the design stage helps ensure that the final protocol not only attends to the science but also reflects what sites and patients consider feasible, acceptable and worthwhile.

KOLs and investigative sites also help build trusted connections and referral pathways. However, while KOLs and investigative sites can be represented by the same person or team, many times they are not. Although KOLs help set scientific direction, it is the investigative site - its infrastructure, staffing and operating culture - that ultimately determines screening velocity, data quality and participant experience. An effective study protocol, therefore, has to work at both levels: it must be scientifically robust and aligned with regulatory expectations, while also fitting the realities of site workflows and patient lives.

At the protocol stage, KOL input can align inclusion and exclusion criteria with what sites can credibly execute and ensure endpoint timing fits routine workflows; this upstream alignment reduces avoidable screen failures and visit deviations when the protocol is translated into site standard operating procedures. During start-up, high-performing sites distinguish themselves through coordinator bandwidth, embedded spirometry and imaging access, established referral relationships beyond their own database, and predictable governance pathways for ethics and contracts.

Even when a KOL is not the principal investigator, their centre can still catalyse referrals by hosting society briefings, sharing neutral study information through departmental channels and mentoring satellite sites on feasibility and pre-screening processes. Once active, site-level discipline - such as regular database refreshes, rapid pre-screen adjudication, consistent patient communications and meticulous endpoint protection - drives sustained enrolment and clean data.

Continued engagement with KOLs supports interpretation of external evidence and provides steering committees with context for operational signals emerging from the site network, but it is the readiness and resourcing of investigative sites that convert a collaboratively designed, scientifically sound protocol into measurable progress on enrolment, data quality and patient experience.

Targeted public-facing campaigns

Public-facing campaigns can expand reach beyond the centre and registry catchment areas when they are tightly governed and clearly informational. Targeted, centrally managed digital outreach can raise awareness among potentially eligible individuals and funnel interested patients toward pre-screening, particularly when content is developed with input from PABs, advocacy partners and investigators (and when clear routing to site-level screening teams is established).

However, public communications about clinical trials and investigational medicinal products must be strictly informational and non-promotional; promotion of unauthorised medicines is prohibited in many jurisdictions. Careful review of messaging, channels and call-to-action language is, therefore, essential to ensure that campaigns support enrolment ethically and compliantly, complementing - rather than substituting for - the work done through local databases and referral networks.

Retention: Minimising burden while maintaining endpoint integrity

Patient retention is a fundamental challenge in small, heterogeneous populations such as AATD, where participants vary widely in disease progression, comorbidities and support systems. Retention hinges on a simple but powerful equation: patients remain in a trial only when the perceived value of participation outweighs the cumulative burden. Time, travel, cost, fatigue, fear of the unknown and conflicting life priorities all compete with that value proposition. Designing for retention, therefore, requires active mitigation of patient burden while rigorously protecting the integrity of primary endpoints.

Operationally, this begins with integrating burden reduction measures into the protocol rather than reacting to dropout signals mid-study. Consolidating procedures into fewer, shorter visits reduces cognitive load and physical strain, which is particularly relevant in AATD, where breathlessness, fatigue and unpredictability of 'bad days' can make travel onerous.

Thoughtful sequencing of on-site procedures to avoid unnecessary downtime further supports retention. For example, decentralised elements - such as home health nursing for non-dosing visits, local laboratory partnerships for routine sampling and remote follow-ups for safety checks - convert what might otherwise be fixed travel costs into flexible, low-friction touchpoints. When governed appropriately, these models preserve visit windows and endpoint precision while materially reducing the personal cost of participation.

Financial and logistical support also play a pivotal role. Predictable, standardised reimbursement for travel and accommodation, transport coordination services and structured reminders help prevent burdens from accumulating into attrition triggers. For patients balancing employment, caregiving or fluctuating symptoms, these supports reduce the 'activation energy' required to stay engaged with the study through its full duration.

Expectation setting is equally important for retention. In AATD, where augmentation therapy may be available, decision-making is often value-driven; some patients prefer the familiarity of standard care, while others are drawn to novel mechanisms or the possibility of improved long-term outcomes. Early, transparent discussion about how participation interacts with standard care - what is substituted, what is added and what happens if the investigational therapy does not meet expectations - reduces the likelihood of mid-study withdrawal prompted by uncertainty or regret. Clear explanation of rescue options, withdrawal procedures and what support is available during retransition to standard care anchors trust and reduces anxiety for both patients and families.

For studies planning an open label extension (OLE), early communication of eligibility criteria, timelines and what participation entails can strengthen continuity. Conversely, if an OLE is not planned, sites should prepare a structured return-to-care pathway, ensuring patients know what to expect after the final visit and how they will be supported during the transition. Closing the loop with participants acknowledges their contribution and reinforces a sense of partnership - the same partnership that improves adherence, data completeness and overall study coherence.

Ultimately, retention in AATD trials is not achieved by any single tactic, but by a coordinated system of burden reduction, transparent communication and patient-centred operational design. When executed well, this approach not only keeps patients engaged but also preserves endpoint evaluability, protects statistical power and enhances the credibility of the final dataset.

Data quality and endpoint protection

In small rare-disease cohorts, a modest treatment effect can be swamped by site-to-site bias or excess within-subject variance. The data strategy should, therefore, aim to minimise systematic error (between-site drift, device idiosyncrasies, rater expectations) and contain random error (day-to-day variability, effort effects). For example, the key issue for spirometry is not merely whether tracings meet acceptability criteria but whether reliability remains stable over time and across centres.

Endpoint protection starts with a clear statement defining precisely which treatment effect is being targeted, in which population, on which variable, at what time point, and how intercurrent events - such as acute exacerbations, use of rescue medication or intercurrent infections - will be handled. Pre-defined operational algorithms then translate these choices into clinic-ready rules (for example, deferring pulmonary-function testing during an exacerbation and repeating within a specified window), which preserves comparability and avoids ad hoc decisions.

Where feasible, central review and near real-time monitoring of key endpoint data (for example, spirometry quality metrics and missing or improbable values) should be embedded in study operations so that drift and variability can be detected and corrected while the trial is ongoing.

Additionally, decentralised elements are valuable only if their measurement properties are equivalent to on-site assessments. That requires a validation step (agreement and repeatability, not just correlation), rehearsal visits to expose connectivity and usability failure modes, and pre-approved fallbacks that keep data on-trajectory when technology stumbles.

Conclusion

AATD compresses all the complexities of rare-disease clinical development: small, dispersed populations; heterogeneous lung and liver pathology; uneven testing and treatment access; and a competitive pipeline that competes for the same clinicians, sites and patients.

In these clinical trials, success is designed in strategy and delivered in execution. In the strategy phase, sponsors that define credible efficacy signals and safety-database needs early, align on jurisdictional expectations and read the competitive landscape create the conditions for feasibility. In execution, those choices must become operational behaviours that reach diagnosed patients beyond site databases, minimise burden without diluting endpoints and protect data with disciplined, risk-based oversight.

Three practical threads bind planning and execution: enrolment, feasibility and evidence.

Enrolment works when neutral, multi-region footprints are matched to testing practices and care pathways - and combined with registry partnerships and compliant public awareness - to convert theoretical prevalence into screenable cohorts.

In terms of feasibility, PABs refine protocols and materials; advocacy networks and KOLs extend trusted referral pathways; investigative sites - with the right staffing and infrastructure - determine whether screening velocity and data quality hold over time.

Finally, evidence stands or falls on endpoint integrity. Clarity about the estimand, principled handling of intercurrent events and an operational posture that actively engineers plausible assumptions give small studies the same inferential discipline expected of larger programmes. Where decentralised elements are employed, their measurement properties must be shown, not assumed.

AATD programmes will always operate close to the limits of sample size and operational tolerance. That is precisely why the most successful trials make early decisions that anticipate regulatory and payer scrutiny, enlist the right people and places to find participants, and execute with a steady bias toward burden reduction and endpoint protection.

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