Lessons Learned from Drug Development Programs in Autism: Implications for Future Programs

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There are no approved drugs for autism core features; the heterogeneous biology, symptom presentation, and clinical outcomes complicate drug trials design, and have hampered therapeutic drug development. We synthesized expert viewpoints from industry and academia on recent diagnostics and biomarker advances as well as pharmacotherapy evidence, aligned to patient-focused drug development outcomes and key concepts. Key learnings include: (i) measure what matters to patients and caregivers; (ii) enrich populations where they can be rationally matched to mechanism; (iii) do not use diagnostic tools as efficacy endpoints; (iv) align biomarker science with a potential qualification pathway associated with relevant behavior and biology; (v) design trials that reduce placebo response, burden, and attrition; (vi) assess co-occurring conditions and treatments explicitly. Observations and recommendations serve as a practical roadmap for sponsors and clinicians to increase trial informativeness and chance of success. **KEYWORDS:** Autism spectrum disorder, treatment outcomes, biomarkers, enrichment, clinical trial methodology, caregiver burden, pharmacotherapy, regulatory science

There is a significant unmet medical need for therapeutic options for the treatment of autism spectrum disorder (ASD). Although risperidone and aripiprazole are approved by the United States Food and Drug Administration (FDA) for the treatment of irritability, a cluster of associated symptoms in ASD, no treatments exist for the core symptoms of ASD. Autism is a spectrum condition, with a wide heterogeneity of clinical symptom presentations and cognitive and functional abilities. This heterogeneity represents a fundamental challenge facing outcome measurement and is a foundational thread passing through all aspects of drug development discussed in this article. Heterogeneity spans biology, behavior, developmental trajectories, language abilities, intellectual functioning, support needs, and co-occurring conditions. Other methodologic issues hamper therapeutic development, including high reliance on self- or caregiver-reported outcomes, oftentimes leading to large placebo effects, as with other central nervous system (CNS) conditions. Lastly, drug development has historically underemphasized the diverse voices and at times heterogeneous priorities of patients and caregivers. An FDA patient-focused drug development (PFDD) for autism meeting report highlighted priorities including better treatments for aggression, sleep, and co-occurring anxiety and mood symptoms, which for some individuals even outweighed the desire for treatments targeting or pathologizing "core" social communication or repetitive behaviors in daily life.

This article aims to identify challenges and pitfalls faced in novel drug development for ASD to date and identify potential paths forward for clinicians and sponsors planning ASD therapeutics for pediatric and adult populations.

METHODS

Comprehensive information was gathered and synthesized from diverse sources, including the following: the FDA's PFDD Voice of the Patient report for Autism;[1] literature reviews of diagnostics and biomarkers; updated ASD pharmacotherapy guidelines and meta-analyses; internal expert interviews, including information from expert consortia and novel biomarker development collaborations such as the Autism Biomarker for Clinical trials (sponsored by the Foundation for the National Institutes of Health)[2,3] and the Autism Innovative Medicine Studies-2-Trials (AIMS-2-TRIALS)[4] consortium (sponsored by the European Innovative Medicines Initiative); and detailed interviews on lessons learned from industry leaders with direct drug development experience.

FRAMING THE THERAPEUTIC PROBLEM: TARGETS, POPULATIONS, AND INDICATIONS

Before discussing endpoints and trial mechanics, we first frame the goals of autism drug development, focusing on the symptom domains of interest, the populations being studied, and the real-world priorities that matter most.

Treat the person, not "the spectrum." A critical success factor for developing effective therapies for autism is adherence to a set of core

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treatment principles. Treatment should focus on the individual rather than "the spectrum," with decisions guided by the specific symptom profile, severity, development stage, and co-occurring condition(s). The field should avoid one-size-fits-all "autism drug" programs that are unlikely to succeed given the considerations above.

Core symptoms vs. co-occurring conditions: clinical and development priorities. Co-occurring conditions should not be deprioritized. For many individuals, anxiety, attention deficit hyperactivity disorder (ADHD), depression, epilepsy, and sleep disturbances drive distress and functional impairment more than core traits. Researchers should align clinical trial targets and real-world care as much as possible. Historical concerns regarding potential "pseudospecificity" of treatment effect are no longer a dominant concern in psychiatric drug development, given an evolution in regulatory perspective.[5] However, symptoms outside current *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5)/International Classification of Diseases (ICD) diagnostic criteria, such as anxiety, hyperactivity and/or ADHD, sensory sensitivity, and sleep disturbances, among others, in individuals with ASD are nonetheless considered important clinical targets by many families and patient organizations.[6] Moreover, there is increasing evidence that pharmacologic treatments developed in neurotypical populations for common co-occurring conditions (such as depression and anxiety) are less effective in autistic individuals, likely due to differences in brain responsivity.[7] Pursuit of potential treatment indications requires thoughtful, early regulatory engagement to assure that development pathways are clearly defined. This will help to head off concerns about nonspecific effects and might also help sponsors navigate the landscape of frequently inadequate trial endpoints. With target domains defined, the next step is aligning ethical and regulatory choices to those targets and populations.

A recent systematic review evaluating α2 agonists[8] (including clonidine, guanfacine, and lofexidine) supports their symptomatic utility in ASD for domains that commonly drive daily burden—particularly hyperactivity, impulsivity, attention deficit symptoms, irritability, and stereotypies—while emphasizing that existing studies vary in size and design and do not define a single standardized treatment protocol. This evidence base is important not because α2 agonists address core ASD features, but because they illustrate a development pathway where (a) symptom targets are clinically meaningful, (b) endpoint selection is naturally aligned to the symptom domain, and (c) tolerability considerations can be anticipated and planned for prospectively.

Principles for care pathways across the lifespan. Clinical care pathways in ASD often diverge from non-ASD standards of care, particularly in medication selection and sequencing. For example, for ADHD, many clinicians consider α2 agonists earlier than stimulant medications (Lurie Center algorithm[9]). For anxiety and depression, they avoid starting with selective serotonin reuptake inhibitors (SSRIs) in many patients with ASD (mirtazapine, duloxetine, bupropion, buspirone are often preferred), as there is evidence that brain response to serotonin modulation might be different in ASD.[7] For irritability (eg, aggression, rapidly changing moods, self-injurious behavior), atypical antipsychotics such as risperidone or aripiprazole remain options and require monitoring of potential metabolic risks and other known potential effects.

Research and clinical development must be grounded in respect for the neurodiversity and autonomy of individuals with ASD. Treatment goals should always include safety, function, participation, and quality of life as targets, not "erasing autism." PFDD perspectives can be woven into benefit-risk frameworks used to evaluate medicines for individuals who are treatment-seeking.

Important sex-specific differences in clinical presentation, care needs, and research participation warrant greater attention in ASD. While autism occurs at a higher frequency in male vs female individuals, this often leads to delay and/or underdiagnosis in female individuals. These differences might have also hampered our understanding of ASD more broadly.[10]

ASD should be approached as a lifelong neurodevelopmental condition, with treatment needs and therapeutic opportunities evolving across developmental stages. Just as earlier behavioral and educational intervention have demonstrated better long-term outcomes and have a strong educational and behavioral rationale, it should be expected that the efficacy of different classes of drugs might be developmental stage– and or age-dependent.

REGULATORY AND ETHICAL FOUNDATIONS FOR ASD DRUG DEVELOPMENT

Regulatory and ethical choices in ASD trials are inseparable from heterogeneity: they shape which populations can participate, how outcomes are interpreted, and whether trials can scale.

Early and iterative regulatory engagement. The complexity of ASD clinical trials, and the need to match symptoms, neurobiology, and testing of novel mechanisms requires early and iterative regulatory engagement. The use of biomarkers for subpopulation identification, target engagement, sample enrichment, or stratification adds to this complexity, requiring early and frequent regulatory engagement. It is recommended that the sponsor or investigator(s) use all regulatory mechanisms to enable dynamic regulatory engagement throughout the trial lifecycle. This includes ongoing dialogue and adaptation (not just pretrial, but throughout) as new clinical outcome assessments (COAs) or digital tools reveal operational or analytic issues—or as external environments shift (eg, FDA/European Medicines Agency [EMA] guidance updates midprogram, novel technological developments).

Early and sustained alignment with regulators on efficacy outcomes and potential indications is essential, exemplified in the case of risperidone (Risperdal) for the treatment of irritability in individuals with autistic disorder, the first approval in the US for use in ASD. During this development program, data from a completed NIH study were utilized,[11] along with a second industry sponsored study, with safety data borrowed from other pediatric programs to bolster short- and long-term safety data. In addition, the FDA requested specific analyses regarding dosing, resulting in ongoing consultation over 2 years. The final indication was not for autism core symptoms, but for irritability, as defined by the Aberrant Behavior Checklist (ABC)-Irritability subscale, the trial's primary outcome. A description of the symptoms defined in the ABC-Irritability subscale was contained within the indication language to help identify who might be appropriate for treatment and what symptoms might respond.

A more recent example is the balovaptan[12] program, which targeted the core symptoms of ASD. In this program, the Vineland Adaptive Behavior Scale-II (VABS-II)[13] was utilized to focus on one aspect of core symptoms, social communication. The endpoint used in the phase 3 program was selected based on evidence of a dose-response on a key secondary endpoint in the negative phase 2 study. The program did not achieve statistical significance in the completed phase 3 study in adults, and a parallel phase 3 study in adolescents and pediatrics was stopped early for futility; however, the approach led to new insights about potential outcome measures for core symptoms, including iterative alignment with regulators on the use of this instrument and interpretation of meaningful change.

Ethical issues in trial design. Given the spectrum of severity, intellectual functioning, and communication, participation in clinical trials of patients with ASD requires a more elaborated and well-defined set of methods for consent and assent. To enable participation across the spectrum, trial designs must balance inclusive consent processes with appropriate protections for highly vulnerable populations. Use of dynamic consent and Institutional Review Board (IRB) innovations may be considered, particularly in cases where the nature of consent might evolve over the course of the study (eg, due to developmental change or to an intervention itself). Granular consent is also an important feature, whereby participants can retain some control over how particularly sensitive datatypes (eg, genetics or audio recordings) may be shared or used beyond the scope of the study itself. Finally, and perhaps most importantly, trials should be codesigned with robust input from patients and caregivers representative of the to-be-treated population—not only to evaluate feasibility, but also to ensure alignment on the value of study procedures with the priorities of the population the trial is ultimately hoped to address.

Prior to trial design, determination of potential outcome measures (eg, symptoms, biomarkers) should always include those with lived experience as well as caregivers, to ensure alignment with all those who are treatment-seeking. Ideally, this means direct patient engagement beyond consultation with advocacy groups, which seek to represent an often-diverse range of perspectives and expectations among their communities. Furthermore, there is a general distrust of medical research within the autism community, owing to the deficit-focused model of autism that is often taken by the medical community, historical harms (see Falk et al[14] and ensuing controversy), the lack of currently available treatment options, fears of inappropriate pathologization or medicalization of merely atypical behavior, the specter of mandatory medication, and the prospect that other support services might be withdrawn if effective medications were found.

Another example of how stakeholder engagement has facilitated clinical development research can be taken from the AIMS-2-Trials consortium. Individuals with lived experience—roles entitled autism representatives (A-Reps)—were an integral part of the research planning committee. A-Reps helped design and direct decision-making for the design and implementation of the research program, the analysis and interpretation of data, communication of results to the stakeholder community, and to balance how results were used to guide subsequent research.[15]

MEASURING WHAT MATTERS: OUTCOME ASSESSMENT IN ASD

Because heterogeneity undermines sensitivity to change, ASD programs succeed or fail on whether endpoints capture meaningful improvement over trial-relevant time horizons.

Limitations of traditional ASD outcome measures. There are fundamental measurement issues with outcome assessment in clinical trials for autism. This has been extensively reviewed over the years,[16,17] but lasting challenges range from the diagnostic origins of most outcome measures to their sporadic use as a long-term marker of symptoms (similar to intelligence quotient [IQ], as a periodic measure of stability). Most clinical outcomes were developed as diagnostic measures (Autism Diagnostic Interview-Revised [ADI-R], Autism Diagnostic Observation Schedule, Second Edition [ADOS-2]) or to periodically document clinical severity of core and associated symptom domains. Widely used clinical symptom scales (eg, Childhood Autism Rating Scale [CARS], Social Responsiveness Scale, Second Edition [SRS-2]) are poorly suited for detecting short-term treatment effects, due to the heterogeneity of symptoms assessed (ie, ranging from), or were not developed specifically for autism (ABC, VABS). These measures do have utility in clinical trials, and there have been recent efforts to develop bespoke outcome measures for use in autism clinical trials (Autism Behavior Inventory [ABI], Autism Impact Measure [AIM]). However, there is further work to be done to understand how to best assess clinically relevant (to researcher/doctor/clinician and to patients and families), short-term outcomes that might be more amenable to measuring outcomes in clinical trials.

Defining meaningful change: functional meaning, minimal clinically important differences. Functional outcome is an important concept in ASD. Measures of functioning and adaptive behavior, such as the VABS,[13] are often used to assess level of care needed or longitudinal progress with treatment. In recent years researchers have tested objective measures, such as skill or performance-based outcomes. The recently finalized FDA PFDD3[18] guidance cautions that performance-based measures might not strongly relate to real-world functional outcomes. More ecologically valid "microsampling" of targeted domains might prove more useful. For example, in the social communication domain, transcripts of verbal exchanges between patient and caregiver might prove more sensitive than decontextualized performance assessments of communication, even if the latter would theoretically be predicted to generalize to a larger range of interaction partners. Social exchange, communication styles and how to measure the ability to communicate well, objectively must consider the approach used and the appropriateness to the audience in social discourse.

It is important to prespecify minimal clinically important differences (MCIDs)[19,20,21] using anchor-based methods (caregiver priorities, daily function) not just distribution-based thresholds. These MCIDs have not yet been defined. This is likely best done in a precompetitive cross-industry consortium model, as this will require significant effort and time to complete. This might need to be done at the symptom domain level and might need to be stratified by age and IQ. Beware of collider effects from unmeasured confounders like sleep and diet, or uncommunicated physical or medical issues, variation in which might acutely affect both autism behavior and physiological/metabolic markers. Measure these confounders to adjust for their effects.

Attributing change when co-occurring conditions drive burden. Core autism symptoms, including social communication and restricted, repetitive behaviors and interests, might be targets for treatment development, but these might not be considered treatment priorities for everyone on the spectrum. Given that these prevalence and severity of behaviors differ across the ASD spectrum, age, and developmental level, it is important to properly identify what is a meaningful change and the feasibility of measuring that change in a time frame suitable for a clinical trial. Moreover, it is important to align therapeutic goals with what families and those with lived experience find meaningful.

Testimony from the PFDD meeting for autism emphasizes the importance of safety, severe mood lability, aggression and self-injury, sleep, anxiety, daily living—and that what is measured by ABC-Irritability might under-represent real-world violence and severe behavioral dysregulation. Sensory hypersensitivity is a common challenge that might impact core features and is commonly linked to the expression of associated symptoms. Comorbid symptoms might also be separate from core symptoms and might worsen outcomes in ASD. ADHD, depression, and sleep and gastrointestinal problems often drive the burden and treatment response signal; the clinical trial strategy taken should attribute effects accordingly by adjusting for the influence of these features.

PRAGMATIC TRIAL DESIGN TO IMPROVE SIGNAL, RETENTION, AND INTERPRETABILITY

Design choices should reduce avoidable variance (placebo and rater effects) while minimizing burden that drives attrition and missingness.

Managing placebo response and rater effects. Several methodologic considerations are relevant for measuring outcome in ASD clinical trials. Placebo effect[22] is common in ASD clinical trials, as are rater-specific issues including rater drift. Such effects can be mitigated with centralized training and certification, blinded central video ratings for validation where appropriate, and screening stabilization periods to reduce regression to the mean and baseline volatility. Expectancy bias and the lack of common lexicon and understanding to describe observed behavior can affect caregiver ratings as well as individual self-report, and clinician drift can also occur due to study procedural effects. The deficit-focused framing[23] of most outcome measures might not only discourage participation but might also enhance placebo responses by directing caregiver attention disproportionately toward perceived deficits. Collectively, these approaches aim to reduce measurement error (rater variance and drift), stabilize baseline severity, and improve interpretability of change by limiting expectancy-driven inflation of symptom ratings. More work needs to be done to develop endpoints not solely based on caregiver or clinician ratings. Most ASD symptom–based measures do not have validated self-assessment forms. There have been efforts to adapt or develop measures for a broader population (including nonverbal and high-support-need individuals).

Population enrichment and stratification. Differential effects of medication can be observed based on age, language ability or IQ, or support needs. It is important to select key variables for stratification or enrichment as appropriate to the target mechanism of action. An example of this can be seen in a differential effect in age group observed in the arbaclofen trials.[24,25] While the overall prespecified analyses did not show a significant benefit, age-based analysis suggested a benefit in older children and adolescents. Children and adolescents might still be receiving extensive behavioral, speech and language, or occupational therapies and school-based interventions, which might allow opportunities for synergistic effects, but might also decrease sensitivity to treatment effects if imbalanced across arms or if these prognostic factors are not properly adjusted for statistically.

Enrollment criteria must be distinct from the primary endpoint to reduce regression to the mean. Complex age standardized assessments can also introduce nonmonotonic artifacts through standardized scoring, thereby diluting treatment effect–related variance. More work needs to be done to develop endpoints not solely based on caregiver or clinician ratings, including measures suitable for nonverbal and high-support-need individuals.

Safety, tolerability, and participant burden. Safety and tolerability are not only ethical requirements but also key determinants of trial retention, missingness, and interpretability in ASD. For many interventions, adverse effects can directly influence caregiver-reported outcomes and functional measures (eg, sedation might change activity patterns and caregiver impressions), making it important to measure tolerability alongside efficacy endpoints and to prespecify how adverse effect profiles will be incorporated into interpretation.

The α2 agonist evidence base in ASD offers a pragmatic illustration of tolerability-aware design. A 2024 systematic review[8] of clonidine, guanfacine, and lofexidine reports promising symptomatic improvements across domains such as hyperactivity, impulsivity/attention deficit symptoms, irritability, and stereotypies, but notes limitations that preclude definitive protocols and emphasize the need to minimize adverse effects. In this context, protocols should incorporate structured monitoring and titration plans for predictable mechanism linked risks (eg, sedation and somnolence as well as autonomic effects), with early monitoring windows and clear dose adjustment guidance to reduce avoidable discontinuation.

Consistent with this principle, the guanfacine extended-release randomized controlled trial[26] in children with ASD reported common adverse events including drowsiness and fatigue, and observed early blood pressure and pulse changes, reinforcing the value of proactive monitoring plans when deploying α2 agonists in ASD trials. More broadly, minimizing participant and caregiver burden—by simplifying visit schedules, reducing redundant assessments, and improving accessibility—can protect data completeness and reduce attrition, particularly in populations with high caregiver demands and sensory or communication needs.

Outcome assessment and trial duration. Clinical trials are time limited by necessity. Outcomes are designed to show change over a clinically relevant time period, while managing the inevitability of dropouts, anticipated clinical effects of a drug, balancing the risks of placebo treatment, etc. For placebo-controlled trials, particularly in early-phase research, duration of study is often limited to 12 weeks, or at most 6 months. However, many of the outcomes pertaining to core symptoms of autism, such as social communication, might require a longer time period than is manageable in the context of placebo control.[27] In addition, some of the behaviors of interest that might be targeted with treatment can depend on environment, such as

availability of social opportunity. Medications might facilitate certain aspects of social behavior but might also require acquisition of new skills to manifest fully, including development of new or deeper, more meaningful social relationships, particularly those outside the immediate home environment. Partnering with nontraditional recruitment channels that might already provide equated background therapeutic support (eg, Cortica) might address ethical, operational, and scientific challenges alike, for example, by better equating patients for access to support, speeding recruitment of treatment-seeking individuals, and mitigating the gene-environment interactions thought to drive additional variance in autism trials.

DIGITAL MEASURES AS SUPPORTIVE TOOLS IN ASD TRIALS

Digital tools can increase measurement density and ecological validity, but only when tied to a clearly defined context of use and meaningful benefit.

Start with the use case, not the technology. Core principles mandate that we start with the "use case" or outcome of interest, not the technology; technology is merely a means to an outcome. Clinical priorities must be used to identify the clinical symptom or concept, the context of use (COU), and decision impact (eg, signal detection in phase 2 vs approach to confirmation in phase 3) before appropriate tools can be selected. Digital technology should ideally be added with defined purpose, even if used in an exploratory manner. This is critically important as each additional measure might increase the potential placebo effect, alongside other factors such as the number of sites, sample size, likelihood of receiving placebo, duration of intervention, and frequency of outcome assessment.[22,28]

Validation and implementation roadmaps. As you develop your research plans, build a "digital validation roadmap" across the development lifecycle. Map out the risks, including analytical validation, feasibility, reliability, validity, sensitivity to change, interpretability, and potential regulatory acceptability. For any digital measure to serve as an assessment of efficacy (whether surrogate, intermediate, or otherwise), it is important to anchor digital signals to outcomes that matter; we must tie the output of novel measures to meaningful benefits for patients (eg, impact on functioning, safety, burden), not merely to diagnostic traits. Content derived from PFDD is one source of what matters to families, but comprehensive exit interviews, direct engagement with advocacy groups as well as individual families, and empirical linkage to overall impressions of improvement are also critical. However, single-point-in-time assessments might not be balanced or reflect the broader ASD ecosystem. The Transcelerate BioPharma Inc. Patient Protocol Engagement Toolkit (PPET)[29] might also serve as a therapeutic area agnostic resource toolkit for patient engagement.

Accessibility and real-world feasibility. Consider how to bridge digital and/or biomarker data to real-world evidence. This often starts by linking these tools to one or more established COAs. Where digital endpoints are combined with clinician- and caregiver-reported measures, methods should be prespecified for handling and interpreting possible discordances between them. Ultimately, the drug effect must improve how the individual feels, functions, or survives. While tools can be used to enrich a population or outcome, ultimately all such tools benefit greatly when they can bridge to real-world evidence or observational data.

Design your trial or program for the anticipated heterogeneity and the population needs for accessibility. Where possible, plan for use of both "bring-your-own-device" and provisioned device options to assure participation is not dependent on access. Consider sensory sensitivities, motor challenges, language or intellectual differences, and the potential need for caregiver involvement. Embed usability pilots upfront of a representative treatment-seeking population, with detailed debriefing where possible to improve troubleshooting and support options.

Developing novel technologies is expensive and time consuming. Where possible, use precompetitive collaboration, either directly or via accessing data or lessons learned. Share or access reference datasets, code lists, and validation packages to accelerate acceptance and reduce single-sponsor risk. Throughout the study and/or program conduct, re-evaluate technologies, including potential ecosystem technological advancement, which could affect or be used to improve on technology in subsequent studies. Do not let historical failures of a technology dissuade subsequent re-evaluation; innovation is outpacing even recent technological limitations. Regulatory compliance with iterative versions of platforms or software can daunting ("predetermined change control plans"), so this should be considered in the transition between phase 1B/2 and phase 3 clinical development, at latest.

Bridging digital signals to meaningful benefit. Experimental digital approaches have been piloted for use in ASD clinical trials, including use of ecological momentary assessment (EMA).[30] The Janssen Autism Knowledge Engine[31] utilized dynamic caregiver-reported outcomes to measure behavior of individuals with ASD in comparison with neurotypical controls using a mobile medical application. Experimental data from EMA approaches on daily caregiver-identified troubling symptoms, mood, and other behavioral approaches were piloted.

BIOMARKERS ACROSS THE DRUG DEVELOPMENT LIFECYCLE

Biomarkers can derisk drug mechanism-of-action and subtyping, but operational and regulatory readiness often might determine whether they can scale beyond early-phase learning.

Roles of biomarkers in ASD. A large focus in the past 2 decades of ASD research is the use of biomarkers[32] to enhance knowledge and understanding of ASD biology. This includes fluid biomarkers, proteomics, genomics, imaging, electroencephalogram,[33] and more bespoke techniques such as eye-tracking during[34] social interaction or observation or electroretinography[35] for target engagement. Biomarkers should be selected for inclusion in mechanistic, hypothesis-driven research to connect underlying biology and clinically relevant behavior to specific drugs or drug targets of interest. Significant progress has been made in genetically linked pathophysiology, or identification of single-gene disorders with high autism comorbidity. When evidence derives from candidate genes, researchers must engage with large, sequenced cohorts to profile potential phenotypes and longitudinal outcomes, using modern sequencing technology (eg, long-read rather than short-read sequencing where possible).

Implementation from early phase to phase 3. There are several technical concerns that must be addressed when using biomarkers

in clinical trials. It is important to think ahead in the development process to determine how biomarker data in phase 2 will inform phase 3. Methodologic components that are required for patient selection, stratification, or measurement over time might need to be validated and carried forward, but the scale of confirmatory phase 3 trials can be expected to complicate a large biomarker footprint. If candidate biomarker tools will be used experimentally at first, plan how easily they might be adapted or scaled for phase 3, including bridging studies if needed. Technical implementation must be systematic and scalable, such that clinical sites that might not have specific expertise could adopt and use the technology. Technological support must be well-provisioned and available across all time zones and hours, with sufficient expertise to resolve most issues. Any part of the system that could break likely will, typically during critical times such as randomization visits. Technical support must be mature and robust, including the ability to troubleshoot remotely.

Data quality metrics and feedback should be developed for the biomarker data collection and provided to sites, ideally in advance of each study visit or data point to be collected. This approach helps mitigate missing data arising from technical failures and participant-related factors. Partnerships with technology providers experienced in ASD, including competitors when they offer superior solutions, should be pursued proactively. Importantly, success with similar biomarker technologies in other clinically defined populations should not be assumed to translate to ASD.

Lessons from consortium and industry programs. Both major autism consortia—the ABC-CT and AIMS-2-TRIALS—have progressed eye-tracking and electroencephalograph N170 response to faces as candidate biomarker endpoints, through extensive interaction with US and European Union (EU) regulators. While both consortium efforts have progressed knowledge and resulted in regulatory discussions, neither are yet qualified by regulators for use, illustrating the challenges and gap between technical promise and regulatory readiness. These approaches still might serve to guide clinical outcome assessment. For example, a phase 2 program run by Johnson & Johnson Innovative Medicine[36] used an experimental biomarker system as a tool for testing methods to stratify or measure outcome. One of the paradigms was a set of eye-tracking tasks[27] shown to be sensitive to individuals with ASD in comparison to neurotypical controls. Stratification on the composite eye-tracking variable was used in a machine-learning based analytic approach to enrich for deficits in social attention; this enhanced treatment effect size in a post-hoc analysis.

TRANSLATIONAL CHALLENGES AND OPPORTUNITIES

The heterogeneity of symptom prevalence and severity of ASD, compounded with the fact that the majority of diagnosed cases lack an understandable underlying cause, has undermined efforts to translate research on treatment and biomarkers from preclinical models to patients. This is not unique to ASD and remains a challenge with other neuropsychiatric indications. In contrast to the idiopathic nature of most ASD diagnoses, there are several well-described monogenic causes of ASD (eg, fragile X syndrome), which although rare diseases, have provided the opportunity for the field to develop preclinical animal models with strong construct validity behind syndrome-relevant phenotypes (behavior and neurophysiology). These syndromic causes of ASD and their respective genetic animal models have been effectively used as a translational tool in evaluating novel drug targets or experimental therapeutics for advancement into clinical trials. However, until clear evidence of beneficial efficacy is confirmed in patients for any drug or drug mechanism, the predictive validity of these models coveted by industry will remain elusive. Similarly, a focus on addressing behavioral phenotypes in animal models has not yielded a robust pipeline of therapeutics to date, and there is increasing emphasis on utilizing cellular (patient-derived) and circuit-based models as translational platforms for drug development in ASD, emphasizing the importance of comprehensive genetic characterization using appropriate sequencing technology when targets are linked to specific genetic variants or families of genes.

SUSTAINING INNOVATION IN ASD DRUG DEVELOPMENT

Sustained progress in ASD therapeutics requires funding models and collaborations that support learning across stages, not just isolated proof-of-concept studies.

Funding models and durability. Funding for research in ASD can be volatile, and it is necessary to stage research and design programs for durability. In addition to traditional investment by private equity and venture capital firms, venture philanthropy of individual donors and innovative vehicle managed by nonprofit foundations have been a common source of early-stage funding of start-up companies in the ASD space. Precompetitive consortia and public-private partnerships help to align priorities, share risk, and standardize methodologies across the stakeholder ecosystem, which can be leveraged to obviate the challenges of direct industry collaborations and infuse much-needed innovation from other sectors, including academia. Private and public funding agency grants and partnerships continue to be the primary driver of research, but they are rarely able to fund across the full translational continuum required to take basic discoveries in the lab into clinical trials. Longer funding horizons and flexibility in program funding, particularly in the early stage, might help to harmonize academic, clinical, and industry incentives.

Precompetitive collaboration and data sharing. Close engagement and partnership with national and international research consortia is critical for small biotechnology companies (or in some cases, large pharmaceutical companies) to sustain clinical development programs in ASD. These are particularly useful if they have a strong training component and multiple industry contributors. Consortia serve as discovery testbeds and capable partners in drug development assessment tool qualification and can be an important source of access to innovation in the field. They might also provide the means to cultivate a trials-ready ecosystem through precompetitive collaborations; the training of next-generation scientists, clinicians, and advocates; and an ability to more fully and flexibly engage with the changing needs of the autism community.

Replication failure is common when moving from proof-of-concept studies to larger, more heterogeneous samples, and this might be expected when attempting to progress models to phase 3 confirmatory studies. Clinical programs for the vasopressin receptor 1A antagonist balovaptan (for ASD) and the gamma-aminobutyric acid/N-methyl-D-

aspartate antagonist arbaclofen[37] (for fragile X syndrome[38] and separately for ASD) illustrate such "effect size erosion" and underscore need for multisite external replicability standards, such as rater consistency or use of blinded raters. It is critical to fully define what must be learned and demonstrated in proof-of-principle, proof-of-concept, and confirmatory studies based on reliable endpoints and sample sizes, and to embed futility analyses or sample-size re-estimation where such factors cannot be fully derisked in advance. Early experience with small open-label safety trials could be helpful for establishing a testable dose and tolerability, but too-small proof-of-concept studies might progress false positives or lead to underpowered late-phase studies, potentially complicating long-term development.

Designing for learning across development stages. Investment in early genetics and clinical outcome registry efforts (eg MSSNG, Autism Speaks; AGRE, Autism Speaks; Simons Foundation Spectrum 10K, SPARK) were only partially successful in facilitating those aims of the research focused on the discovery of novel drug targets and better endpoints. This was in part due to the additional complexity in ASD revealed by these consortia's work, rendering sample size deficiencies and associated challenges with sustainability of the initially planned investments. This repeated lesson can be mitigated with a greater upfront emphasis on interoperable data, curation, and linkage to outcomes and crowd sourcing of data in large, diverse datasets including re-analysis with rigorous governance. Data sharing in a precompetitive environment to learn from recent and historical trials, even limited to baseline characteristics and clinical profiles, could assist with predictions for understanding longitudinal outcomes and more efficiently discover prognostic markers and signs/symptoms.

While there might be a temptation to utilize umbrella trial designs to share placebo and reduce costs, a precision-focused approach might ultimately prove more effective. Heterogeneity in ASD might penalize broad designs. Enrichment based on biomarkers and behavioral phenotypes might allow for more focal tests of a mechanistic hypothesis but might also require extended validation timelines and might also be counterproductive where these strata have an uncertain link to the mechanism under study. Alternatively, biomarkers could be employed in a broader "all comers" trial to be used as exploratory stratification factors to motivate subsequent confirmatory test in a mechanistically enriched population. In light of these unknowns, there is clear benefit in designing and testing biomarkers and outcome measures where incentives can be aligned with technology partners and others with differentiated business models. Industry technology (eg, big-tech engineering) can accelerate validation of digital measures where methods are open, and COUs are relevant to regulators and patients alike.

With expansion of omics-focused research, pathways must be found to accelerate the translational research these techniques enable. Translational validity of work preclinically (eg, target selection, validation, compound evaluation) is perhaps one of the most challenging issues facing early development of treatments for idiopathic ASD. Investors favor the reduced risk profile of programs with a clear connection to genetically defined subgroups or known pathobiology (monogenic syndromes) over programs focused on idiopathic ASD, when evaluating opportunities for new investment. Additionally, the opportunity landscape favors programs with features overlapping other indications such as schizophrenia or epilepsy, where established pathobiology and validated development pathways derisk investment—further disadvantaging idiopathic ASD programs that lack these reference points.

DISCUSSION AND CONCLUSION

There have been major advances in understanding of the neurobiology of ASD, resulting in identification of novel targets for ASD treatment development, and enhancing signal detection in drug development research for ASD. Better appreciation and engagement with individuals with lived experience and caregivers is now common across all stages of research. Identifying treatment targets that are meaningful to individuals with ASD, in partnership with the community, has led to greater acceptance of research and more targeted, relevant clinical approaches in novel therapies. Precompetitive consortia, advocacy, public funding sources, academia, and industry have begun to form more creative partnerships, to help advance the ecosystem for drug development in ASD. This includes responsible approaches to funding of research, including assurance of continuity of funds to complete research projects once initiated.

Greater understanding of the limitations of existing outcome assessment approaches is leading to development of new measures, combined with novel drug mechanisms and symptom- and subgroup-specific biomarkers. Use of biomarkers tied to disease biology, symptoms and behaviors has become more mainstream and more feasible in clinical trials. There are now multiple examples of successful use and scaling of biomarkers in clinical trials to help with population enrichment and with signal detection. The emerging evidence base for α2 agonists in ASD provides a pragmatic example of how symptom-focused strategies can be informative and clinically meaningful: benefits appear most consistently in behavioral regulation domains (hyperactivity and impulsivity, irritability, stereotypies), reinforcing the importance of endpoint domain fit, prespecified attribution plans across correlated symptom domains, and proactive tolerability monitoring as a retention and interpretability strategy.

Continued expansion of these critical success factors will ensure a higher yield of successful studies and better, more targeted treatments for ASD. Using these principles and building on recent experience, we can derisk future programs, create a more sustainable ecosystem for clinical drug development, and ultimately produce novel therapies that improve the lives of individuals with ASD and their families.

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