Points to consider when initiating clinical investigations in autistic paediatric populations—A White Paper

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ABSTRACT

Many individuals with autism spectrum disorder (ASD) experience various degrees of impairment in social interaction and communication, restricted, repetitive behaviours, interests/activities. These impairments make a significant contribution to poorer everyday adaptive functioning. Yet, there are no pharmacological therapies to effectively treat the core symptoms of ASD. Since symptoms of ASD likely emerge from a complex interplay of vulnerabilities, environmental factors and compensatory mechanisms during the early developmental period, pharmacological interventions arguably would have the greatest impact to improve long-term outcomes when implemented at a young age. It is essential therefore, that clinical development programmes of investigational drugs in ASD include the paediatric population early on in clinical trials. Such trials need to offer the prospect of direct benefit (PDB) for participants. In most cases in drug development this prospect is supported by evidence of efficacy in adults. However, the effectiveness of treatment approaches may be age-dependent, so that clinical trials in adults may not provide sufficient evidence for a PDB in children. In this white paper, we consolidate recommendations from regulatory guidelines, as well as advice from the Food and Drug Administration, USA (FDA) and the Committee for Human Medicinal Products (CHMP) consultations on various development programmes on: 1) elements to support a PDB to participants in early paediatric clinical trials in ASD, including single-gene neurodevelopment disorders, 2) aspects of study design to allow for a PDB. This white paper is intended to be complementary to existing regulatory guidelines in guiding industry and academic sponsors in their conduct of early paediatric clinical trials in ASD.

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1. Introduction

Autism spectrum disorder (ASD) is defined by core symptoms in two domains, (1) persistent deficits in social communication and social interactions, and (2) restricted, repetitive patterns of behaviour, interests or activities, and differences in sensory reactivity (American Psychiatric Association [APA], 2013). The severity of these symptoms can vary significantly from one individual to another. Alongside these core symptoms, other psychiatric and neurological conditions are frequent, including intellectual disability, epilepsy, attention deficit hyperactivity disorder, depression and anxiety (Lai et al., 2019; Simonoff et al., 2008). ASD arises from a complex interaction between genetics and the
environment with some conditions having a clearly defined genetic link, e.g. Fragile-X, Rett syndrome, Tuberous sclerosis, Dup15q syndrome, Phelan-McDermid syndrome. Autism is a life-long condition with diagnoses often made in the toddler years, but sometimes not until later childhood or older. Many individuals with ASD exhibit a delay in achieving development milestones associated with the core domains. Deficits in social interactions manifest as delayed and reduced interactions with peers, reduced or absent sharing of enjoyable experiences and interest with peers, and lack of social judgement. Impairments in communication include a delay in verbal language development, impaired expressive language, deficient language pragmatics, and impaired use of non-verbal communication. These impairments in social interaction and communication, make a significant contribution to poorer everyday adaptive function in ASD (Tillmann et al., 2019). Throughout their lifespan, individuals with ASD continue to demonstrate significant impairments in different aspects of adaptive function, with the gap in social and communicative functional skills relative to same-age typical peers becoming increasingly larger as individuals with ASD move into adolescence and further into adulthood (Chanham et al., 2018). These adaptive function impairments predict real-world outcomes in ASD, including educational attainment (de Bildt et al., 2005) and the likelihood of independent living (Parley et al., 2009; Paul et al., 2004). Therefore, it has been argued that the paediatric population would likely benefit from an early intervention to improve social and communication symptoms relevant for adaptive skills (Diaz-Caneja et al., 2021), which may ultimately translate into improved outcomes and better quality of life.

At present, there are no psychopharmacological therapies to effectively treat the core defining symptoms of the disorders. Early diagnosis of autism is believed to be instrumental to ensure early access to non-pharmacological supports and with that increased chances for a favourable long-term outcome (Gabbay-Dizdar et al., 2022; Bradshaw et al., 2015). The primary model of non-pharmacological treatments are developmental and behavioural, with the aim to improve an individual’s ability to learn and improve basic social-communicative behaviours (e.g. joint attention, gestures) and dyadic communication and interaction. However, because of considerable variation between different intervention models in intervention components, length, intensity, and mode of delivery, as well as lack of clinical trials, the strength of evidence to support any of these non-pharmacological treatment approaches is still limited.

Depending on the therapeutic target and symptoms of interest, initiation of treatment of ASD symptoms or other neurodevelopment disorders during adulthood may have limited or no benefit, as the brain has significantly less plasticity compared to the early years of development. Also, some developmental concepts may have critical time windows during which change becomes less likely. For example, language development is considered to depend on a critical development period leading up to 5 years, which makes acquisition of speech and new language milestones beyond the age of 5 years less likely (Pickett et al., 2009).

The Addendum to International Council for Harmonisation (ICH) E11: Clinical investigation of medicinal products in the paediatric population addresses the question of the timing of paediatric studies during development. In this guideline it is acknowledged that paediatric studies should be undertaken early on for conditions that predominantly or exclusively affect paediatric patients or for serious/life-threatening conditions affecting both adult and paediatric patients for which there are limited treatment options. However, for other conditions the guideline recommends initiation of paediatric trials post phase 2 in adults, owing to the high attrition rate of new chemical entities during phase 1 and 2 clinical development in adults, thereby preventing needless exposure of the paediatric population to an investigation drug without benefit. ICH E11 is a general guideline and does not provide specific recommendations for any given condition. As such, it does not take into account that a potential benefit of a therapeutic agent in an autistic paediatric population may not be observed when initiating treatment in an adult population because of the different development trajectories. The Committee for Human Medicinal Products (CHMP) guideline, on the clinical development of medicinal products for the treatment of Autism Spectrum Disorder (ASD), EMA/CHMP/598082/2013, provides guidance on the conduct and design of clinical trials in autistic populations. It encourages sponsors to study the effect of novel therapies in children with ASD as early as possible and, depending on the mode of action and properties of the product, study children as young as possible if it is likely that they will benefit from early treatment.

At the time of writing of this White Paper, the Food and Drug Administration (FDA) issued a draft guidance for public consultation Ethical considerations for clinical investigations of medicinal products involving children, September 2022. The aim of FDA’s guidance is to provide clarity to sponsors and IRBs on providing evidence for the prospect of direct benefit to trial participants and on risk categories for interventions or procedures where no prospect of direct benefit is expected.

The prospect of direct clinical benefit in a paediatric population is an important ethical consideration before initiating a clinical trial and is required by EU and US regulation – EU No. 536/2014, article 32 and the 21 CFR 50, subpart D.

In this White Paper, we aim to provide guidance to sponsors and investigators on the conduct and timing of clinical trials in paediatric populations with ASD and developmental disorders presenting autistic features. These recommendations are intended to be complementary to the ICH, CHMP and FDA guidelines. Drug development design standards and strategies for ASD are still a developing field. Compared to other neuropsychiatric indications the field lacks standards for core aspects of the design of intervention trials such as endpoint selection and definition of the target population due to the comparably lower number of drug development programs and, most importantly, the lack of success of previous development efforts for core symptom treatment which are needed to define and inform guidelines for the field.

We have reviewed scientific advice from multiple development programs in idiopathic ASD and syndromic autistic conditions received from CHMP and FDA as well as regulatory feedback on paediatric study protocols. We attempt here to consolidate the considerable body of regulatory advice into recommendations on the conduct and timing of paediatric trials during development. We will address specifically (i) the need to provide a prospect of direct benefit to study participants, (ii) considerations on the target population and community engagement (iii) confidence in the biology, in particular evidence provided by cellular and animal models of ASD, (iv) study duration, dose selection and choice of endpoints, (v) statistical considerations and safety monitoring.

With these recommendations, we aim to improve the quality of clinical research in ASD and related neurodevelopment disorders and facilitate the initiation of trials in an age-specific population which is likely to be more responsive to potential therapeutics and thereby gain the greatest clinical benefit.

2. Development programmes reviewed

In developing our recommendations on the conduct of early clinical trials in a paediatric ASD population, we have reviewed FDA advice, CHMP scientific advice and other regulatory comments on study protocols from development programmes shown in Table 1. The regulatory advice received on these development programmes is not in the public domain. While the list of programmes assessed here is not fully comprehensive, they cover the spectrum of risk categories and are programmes that reached at least phase II clinical development sponsored, or previously sponsored, by members of the AIMS-2-Trials consortium (https://www.aims-2-trials.eu/). Specific advice on each programme is not provided as this information is proprietary.
Table 1
Development programmes reviewed.

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<thead>
<tr>
<th>IMP</th>
<th>IMP description</th>
<th>Target population</th>
<th>Sponsor</th>
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<td>Balovaptan</td>
<td>V1a antagonist</td>
<td>ASD</td>
<td>F. Hoffmann-La Roche</td>
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<td>FAAH inhibitor</td>
<td>ADSD</td>
<td>Janssen Pharmaceuticals</td>
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FAAH, fatty acid amide hydrolase; GABA-A\(_\alpha\)5, \(\gamma\)-aminobutyric acid-A\(_\alpha\)5 receptor negative allosteric modulator; GABA-A\(_\alpha\)5 PAM, \(\gamma\)-aminobutyric acid-A\(_\alpha\)5 receptor positive allosteric modulator; GABA-B, \(\gamma\)-aminobutyric acid-B receptor; mGLur5, metabotropic glutamate receptor subtype 5; UBE3A LNA, ubiquitin protein ligase E3A locked nucleic acid; V1a, Vasopressin V1a receptor.

3. Prospect of direct benefit

The Additional Safeguards for Children in Clinical Investigations (21 Code of Federal Regulations [CFR] 50 Part D) provides provisions for the inclusion of minors in a clinical trial, accounting for the potential risk to trial participants, the prospect of direct benefit (PDB) and the degree in which monitoring procedures may contribute to the well-being of study participants. The FDA draft guidance Ethical considerations for clinical investigations of medicinal products involving children, September 2022, while not legally binding represents FDA’s current thinking on how industry, sponsors and Investigational review boards (IRB) can best comply to 21 CFR 50, including subpart D. It has been our experience that for new investigational drugs under development for ASD, where there has been limited clinical experience in adults, FDA have generally applied the provisions of 21 CFR 50.52, i.e. the interventional clinical trial poses a greater than minimal risk to minors and therefore must provide a PDB for the study participants. The risks must be justified by the expected benefit and the expected risk-benefit profile must be at least as favourable as that presented by accepted alternatives.

Similarly, the European Union (EU) Clinical Trial Regulation No. 536/2014 Art. 32, Clinical trials on minors, requires that there are scientific grounds for expecting that participation in the trial will produce: (i) a direct benefit to the minor concerned outweighing the risks and burdens involved, or (ii) some benefit for the population represented by the minor concerned and such a clinical trial will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor’s condition.

FDA and European regulatory agencies use multiple factors to assess the PDB, including (i) non-clinical data from animal models, (ii) clinical proof of mechanism and/or concept data from adults, (iii) data to support that the proposed dosages are likely to have the intended treatment effect, (iv) evidence to support that the trial treatment duration is sufficient to have impact on a meaningful clinical outcome, and (v) the individuals planned for enrolment are likely to benefit from treatment. Whether the PDB outweighs the risks is determined with consideration to non-clinical toxicology data, adult safety data, and the safety monitoring measures specified in the study protocol.

4. Paediatric study populations and community involvement

The CHMP guideline, on the clinical development of medicinal products for the treatment of Autism Spectrum Disorder (ASD), EMA/CHMP/598082/2013 provides valuable guidance on diagnosis, inclusion and exclusion criteria. Furthermore, it encourages sponsors to study the effect of novel therapies in children with ASD as early as possible and, depending on the mode of action and properties of the product, study children as young as possible if it is likely that they will benefit from early treatment. It is our view that the PDB and arguments for a favourable risk-benefit profile are more compelling in a population with phenotypes substantially impacting their quality of life. A specific threshold on such phenotypic measures may be set as inclusion criteria for entry into the study to ensure target symptoms are chronically present or sufficiently severe prior to baseline, and therefore might benefit from drug treatment. A framework for implementing a precision medicine approach to neurobehavioural disorders has been well described by Lenze et al. (2021) and Beversdorf et al. (2023). Whenever possible, Sponsors should aim to deploy putative biomarkers in early trials to identify more biologically homogeneous subgroups within the autism spectrum based on, e.g. electrophysiological, neuroimaging, molecular, and biochemical variables. Post-hoc analyses may identify enrichment or stratification markers to be employed prospectively in pivotal trials as treatment-predictive biomarkers. Such precision medicine approaches may help to identify subgroups within the ASD spectrum with high sensitivity to the studied mechanism of action (MOA) (Loth et al., 2016). The level of evidence for the use of such biomarkers in a specific program and its scientific rationale for their deployment in early-stage studies is an important aspect of the benefit-risk assessment and the choice of target population as it directly relates to the prospect of direct benefit of a group of study participants.

It is our general recommendation that study populations be as homogeneous as possible in terms of underlying pathophysiology. As such, syndromic forms of ASD should be studied separately in dedicated studies, unless otherwise justified. In idiopathic ASD, populations with distinct co-occurring conditions, such as intellectual disability, epilepsy, etc., should either be studied in separate trials or stratified within the same trial. The description of the study population should include the degree of severity of the target symptom(s) or degree of overall impairment, which needs to be supported by epidemiological data.

While it is important in the planning of any trial to consult with the affected community, we think it is critically important to do so in ASD. The autism community is enormously diverse, with widely varying degrees of unmet medical needs. This diversity is enriched by a network of self-advocates which have varying familiarity with (and interest in) biomedical research including clinical trials. In our experience, early consultation with the community representatives on the proposed study design, including entry criteria is critical for success in this area.

5. Confidence in the mechanism of action of the investigational drug, including evidence from animal models

FDA and CHMP have both acknowledged that building evidence for PDB in children from adult data may not be feasible. In such cases, data from cellular and animal models may be a viable alternative for providing evidence for PDB. These complementary models can interrogate target engagement, connect the target to restored cellular function, and ultimately demonstrate therapeutic benefit at an organismal level. When used together, these models can increase confidence in the MOA and PDB.

The availability of human induced pluripotent stem cells (iPSCs) has unlocked the ability to study neurodevelopmental disorders in a human cell model. Given the larger divergence of the human central nervous system from animal models, in comparison to other organ systems, these models may be of high value for neuropsychiatric conditions. Furthermore, because iPSCs are derived from human-samples, disorders with
complex genetic aetiologies can be more easily modelled. These human subject-specific genetic aberrations are particularly important for evaluating genetic medicines, which may target DNA sequences that are not conserved between human and rodent. For instance, iPSC-derived neurons from individuals with Angelman syndrome identified electrophysiological phenotypes (Fink et al., 2017) and enabled identification of antisense oligonucleotides targeting a non-conserved non-coding RNA to restore UBE3A mRNA and protein expression (Dindot et al., 2022). New technologies for converting iPSCs to neurons and three-dimensional cultures make these cellular models increasingly amenable to high-throughput screening. Despite the advantages of using relevant human cell types for discovery, there are still gaps left by this model system. iPSC-derived neurons are more similar to foetal neurons and robust differentiation strategies exist for only a few neuronal subtypes. Human neuron models also do not have appropriately developed circuitry and readouts that can be connected to an autistic individual’s benefit. Furthermore, iPSC-derived neurons do not allow for studying biological mechanisms in the regulation of social interaction, restricted and repetitive behaviours and sensory information processing. Therefore, animal models should be considered to complement these sophisticated in vitro models.

A multitude of animal models for ASD have been generated in the last decades, reflecting various genetic and/or environmental components implicated in human aetiology. The species of choice is typically in rodents, and most-often in mice, given the relative ease of inducing genetic modifications, and their well understood physiology and behaviour in the laboratory environment. More recently, rat models and non-human primate models (Zhou et al., 2019) have become more visible. However, the limited availability of non-human primates and ethical constraints regarding their use in Central Nervous System drug research and development will likely prevent their utility for studies of PDB.

The predictive validity of the animal model for PDB will be increased when it presents both a clear construct and face validity, and when the observations are sufficiently robust and reproducible to enable the study of treatment intervention. Animal models with high construct validity have been generated for several rare syndromic forms of ASD, given that they have clearly identifiable genetic mechanisms. Notable examples include Ube3a mutant mice for Angelman syndrome (Rotaru et al., 2020), MeCP2 knock-out mice for Rett Syndrome (Lombardi et al., 2015) and fmr1 knock-out mice for Fragile X Syndrome (FXS). The predictive value of such models for ‘symptomatic’ treatments however has generally been poor (e.g. multiple failed trials in Rett Syndrome and FXS). There are likely a multitude of reasons underlying this failed translation. One critical point may be the limited conservation of biological mechanisms underlying rodent endpoints measured in preclinical studies, to the human behaviour measured in clinical trials. Both improvements in the study of rodent ‘endophenotypes’ and new tools applied in the clinical setting may aid future successful translation. It is also assumed that genetic rodent models hold more predictive power when the treatment intervention is more proximal to the underlying genetic cause, e.g. for therapies aiming at a genetic rescue of Ube3a, MeCP2 or fmr1. Ongoing clinical studies in this domain will be critical to understand the predictive validity of these models.

For idiopathic ASD with unknown aetiology, or where the cause likely depends on a complex mix of genetic and environmental factors, an animal model with construct validity cannot be created. In this context, other models have often been chosen because of their face validity, e.g. pharmacological observations that appear analogous to the symptomatology of the human condition. Examples in this case include BTBR T+J Imp2f/J (BTBR) mice (Bolivar et al., 2007; Moy et al., 2007; Nadler et al., 2006), which are reported to show repetitive behaviour, and models that take inspiration from environmental factors implicated in ASD such as prenatal valproate exposure (Schneider and Przewlocki, 2005) or maternal immune activation (MIA, Lammert and Lukens, 2019). The relevance of these models for children with idiopathic ASD is less clear, especially given the large heterogeneity within this population. Successful prediction is likely to be increased when a clear stratification marker can be identified.

Coupled to the animal models are a plethora of assays developed to measure function, which are typically focused on core and co-morbid symptom domains in ASD (e.g. sociability, repetitive behaviour, cognition, and motor skills). As mentioned above, such endpoints must be used with caution for predicting human PDB, particularly when there are large inter-species differences in mechanisms underlying the behaviours. More recently, functional biomarkers (e.g. electroencephalography and magnetic resonance imaging) that can measure so-called ‘endophenotypes’ have been introduced into research in pre-clinical ASD models (Janz et al., 2022; Zerbi et al., 2021, 2022). These endpoints may hold greater promise for prediction of PDB in that they can be used similarly in the clinical setting, and their relationship to symptom severity and underlying mechanisms can be more readily explored in the nonclinical setting.

The majority of the aforementioned assays have been established in the adult or late adolescent rodents. However, largely for practical reasons, the use of functional endpoints in early developing and juvenile rodents is often restricted to studies of gross neurological function (e.g. the presence of a righting reflex) and developmental milestones (e.g. date of eye opening), which often have poor sensitivity for detecting treatment effects and may hold little translational relevance to the human condition, for reasons already mentioned. This raises an additional challenge concerning the age of the animals in which the studies supporting PDB should be performed. The value of studies conducted exclusively in adult animals for the demonstration of PDB in a paediatric population may be limited, in particular for therapeutic interventions that aim to address the underlying disease mechanism rather than behavioural symptoms. An alternate strategy is to commence treatment intervention in early postnatal or juvenile animals and perform subsequent monitoring of functional endpoints with high translational confidence in the adult animal.

Animal studies have shed light on the concept of a ‘critical window’ for treatment intervention to be effective (Marin, 2016). In some examples, it is clear that early intervention leads to the greatest gains in efficacy (e.g. Ube3a, O’geen et al., 2023). On the other hand, some studies suggest that functional recovery remains possible even with treatment in adult animals (e.g. MeCP2 Knock-out mouse, Ure et al., 2016). Understanding the optimal time point for intervention will come from a solid biological understanding of the role of the particular target in aspects of brain development and/or maintenance and is likely to vary considerably between different target biology. Careful comparison between the role of the target biology in humans is also necessary to increase confidence that findings in pre-clinical species are likely to translate.

In summary, animal models can be valuable to generate hypotheses to test in subsequent clinical studies, particularly around optimal timing of treatment intervention and likely PDB. However, as we have outlined, there are challenges associated with translational research from animal models to the human population, particularly in the context of ASD. An unclear aetiology in a very large part of the human ASD population and a strong age-dependent component of neurodevelopmental disorders, makes faithful modelling of the disorders in animals challenging, if not impossible. Moreover, behaviours impacted in ASD (i.e., social interactions and communication, and restricted repetitive behaviours) are complex and likely highly divergent between rodents and humans in their underlying mechanisms. This presents further challenges to translational research from animal models to human populations. Key to increasing successful prediction of PDB are 1) animal models that accurately reflect the aetiology of the human condition whenever possible (i.e. have clear construct validity in the case of syndromic forms of ASD), meaning that confidence in the mechanism of action should first and foremost come from human biology (Karlsson et al., 2019), 2) deploying translational endpoints that are proximal to the target and disease biology, and 3) having a solid understanding in the
developmental role and relevance of the target in both the preclinical species and human biology, to guide the rationale for optimal timing of intervention. Human iPSC models are complementary to animal models and allow the study of target engagement and have the potential to connect the target to restored cellular function.

6. Study duration and dose selection in first-in paediatric ASD studies

Proof of concept studies which need to provide a PDB need to be of sufficient duration to allow for a meaningful clinical treatment effect. Our experience over multiple programmes is that these studies should be of at least 12 weeks treatment duration, however, longer durations may be required depending on the drug target and objectives of the study. A 12-week treatment duration is proposed to allow a sufficient treatment duration to characterise the safety and tolerability profile in paediatric participants, as well as provide potential benefit from the treatment without causing excessive burden to the participants and caregivers. A shorter treatment duration may not be able to provide substantial benefit given that improvement in the core domains may require sufficient learning time to improve the specific skills and behaviours. This applies particularly to communication and socialisation skills.

Conceivably, with the advent of more sensitive measures (whether clinical outcomes or surrogates thereof), shorter ‘fast-fail’ studies might be possible in the future where those measures have been appropriately qualified by regulators (see also below, Study endpoints section).

The dose should be demonstrated to be safe and well tolerated in adult phase 1 clinical trials and needs to be sufficient to produce an expected clinically meaningful treatment effect. Evidence for this may come from animal model data and clinical data in adults. If a pharmacodynamically active dose is identified from phase 1 clinical trials, age-relevant doses must be determined to ensure equivalent systemic exposure in paediatric groups when compared to adults.

7. Study endpoints

As outlined in the CHMP guideline, on the clinical development of medicinal product for the treatment of Autism Spectrum Disorder (ASD), EMA/CHMP/598082/2013, study endpoints to assess efficacy should demonstrate a treatment effect on at least one core symptom which should be supported by a positive effect on functioning. Clinical outcome assessments (COA) rated by observers (e.g. parents) or clinicians which assess core concepts such as social communication and restricted, repetitive patterns of behaviour, interests or activities are therefore often used as endpoints for decision making in ASD paediatric studies. While there has been an emergence of self-reported scales in paediatrics, 12 years and older is generally considered to be an appropriate age for self-report in children without intellectual disability (Arbuckle and Abetz-Webb, 2013). The appropriate respondent should ultimately be decided upon based on the concept being measured and the functional skills of the individual.

When selecting a COA, the FDA draft guidance Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for Purpose Clinical Outcome Assessments, June 2022, highlights the importance of fully understanding the condition and obtaining perspectives from the paediatric population. The FDA Voice of the Patient Report, Autism (January 2018, https://www.fda.gov/media/111099/download) provided insights regarding the most important concepts to measure, with communication difficulties and behavioural issues (e.g. violent, aggressive, self-injurious behaviours, etc.) identified as having the most significant impact on daily life. Cognitive difficulties, social impairments, difficulty adjusting to changes in routine, restricted interests and other issues with sleep, gastrointestinal symptoms, allergies, and extreme overactivity were also raised. These findings are mirrored in other research such as the development of a conceptual model which documents the symptoms and impacts of relevance in children, adolescent and adult autistic populations (McDougall et al., 2018). Example endpoints in paediatric autism populations have therefore typically focused on core symptoms, adaptive behaviour, functioning and broader health-related quality of life which remains an important concept for reimbursement bodies (EUnetHTA draft guideline Health-related quality of life and utility measures, 2015). These concepts are important to assess in clinical trial endpoint measurement strategies depending on the therapeutic MOA and functional severity of the population, ensuring selected COA are capturing meaningful concepts in the specific paediatric context of use under investigation. Novel personalised outcomes may also be needed with examples of goal attainment scaling type approaches being used with success in Fragile X (Berry-Kravis et al., 2020). Ensuring psychometric validation of COA (i.e., validity, reliability and sensitivity to change) in the specific population is also critical before implementing a scale in a study.

However, despite the clear understanding of what is relevant to measure in paediatric ASD and the blueprint from health authorities with respect to validation standards, many challenges with the selection and interpretation of COA in the paediatric population exist. Clinical heterogeneity is a key challenge in ASD (Masli et al., 2017) and other developmental disorders displaying autistic features such as Fragile X (Jacqumont et al., 2013), Dup15q syndrome (DiStefano et al. 2020) and Angelman syndrome (Willgress et al., 2021). The clinical presentation of core symptoms and functional ability is often variable due to confounding factors such as genetics, comorbidities and environmental factors, which makes the selection of a single outcome measure across a paediatric population, highly challenging. In addition, demographic factors such as age and sex can add complexity in ensuring outcomes are appropriately validated. Clinical trials have therefore recently focused on defining more homogeneous subgroups in order to increase the potential to detect treatment efficacy. More objective measures such as neuropsychological batteries and biomarkers, that may be related to the MOA of the investigational medicine (e.g. EEG 1/F and GABA-A), can facilitate the identification of potentially homogeneous subgroups, which in turn can help to select meaningful outcome measures which are sensitive to change in a well-defined population.

The scoring of the endpoint is also critical in detecting a treatment effect. Many COAs assessing core symptoms and functioning focus on change in raw scores (e.g., Autism Impact Measure, Autism Behavior Inventory, Repetitive Behaviors scale Revised, Childhood Routines Inventory-Revised, global impressions, etc.). However, for certain scales such as the Vineland-3™ and Bayley-4™ which assess adaptive behaviour and key developmental domains respectively, alternative scoring metrics including standard, age equivalent and person ability scores (e.g. Growth Scale Values) are available. Recent research (Eisengart et al., 2022; Farmer et al., 2020) has highlighted both the limitations of norm-referenced scores such as standard scores (e.g. lower reliability at the tails of the distribution which can lead to floor effects in neurodevelopmental populations), as well as the advantages of person ability scores over normative scores. These advantages include equal interval scoring, assessment of absolute change (not relative change as standard scores), availability of conditional standard errors of measurement, and better effect size recovery (Daniel and Vannier. 2022; Farmer et al. 2023). Such developments in scoring may allow for enhanced signal detection in paediatric developmental conditions and are strongly encouraged to be used in future studies instead of standard scores.

Age equivalent scores are measured at the ordinal level which introduces issues in measuring change, are less sensitive to change (e.g. several raw score points can correspond to a single age equivalent score) and they do not have an equal interval scale.

8. Statistical considerations and safety monitoring

As paediatric populations typically represent vulnerable individuals, dedicated safety monitoring during the conduct of a study is recommended, and usually requested by health authorities and ethics
committees. Especially in studies where dosing of the investigational drug is not yet established, set up of an internal monitoring committee (IMC) with external scientific oversight or, alternatively an independent data monitoring committee (iDMC) is advised if not demanded by regulatory authorities. If in dose escalation studies, the constitution of a dose escalation team is preferred, the scope of this team needs to be broadened to include safety monitoring in order to avoid the constitution of a separate, dedicated safety committee. Like for IMCs and iDMCs, the arising ‘safety monitoring and dose decision board’ should be guided by an agreement or charter.

Powered studies in a paediatric population from a first perspective are designed in a way that is comparable to studies in an adult population. As the sample size of a powered study is crucially dependent on the variability in the data on one hand and on the assumed true effect size on the other hand, there should be a discussion in the preparation phase of the study whether the primary endpoint and the anticipated product profile are adequate for a paediatric population or whether these have to be tailored. Often, historical data (whether in-house or external) from an adult population is used to provide estimates on the ‘minimally clinically important difference’ or psychometric properties of the primary endpoint. There should be a discussion whether insights from such data and psychometric properties in general are transferable to the paediatric population. Mitigation strategies to cope with clinical heterogeneity, such as subgroup analysis should be taken into account.

9. Conclusion

As children are regarded as a particularly vulnerable population who cannot consent themselves to participate in a clinical trial, additional regulatory and ethical safeguards are in place to minimise risks to their participation. Should an investigational drug pose a greater than minimal risk, then it is required that Investigational review boards/Ethics Committees find that the risk is justified by the prospect of direct benefit. In ASD clinical research this is particularly challenging because (i) the population, other than presenting autistic traits, is generally healthy and the threshold for risk is low, and (ii) efficacy data from adult ASD trials may not reflect the potential benefit in children or adolescents. In this white paper, we have reviewed available regulatory guidelines, FDA advice, CHMP scientific advice and other regulatory comments on study protocols to provide recommendations on how to best provide a prospect of direct benefit in a paediatric study protocol for the treatment of ASD symptoms. These key aspects are summarised below:

<table>
<thead>
<tr>
<th>Design aspect</th>
<th>Considerations</th>
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</thead>
<tbody>
<tr>
<td>Study population</td>
<td>Populations should be as homogeneous as possible</td>
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<td></td>
<td>Study syndromic forms of ASD separately to idiopathic ASD</td>
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<td></td>
<td>Stratify or study separately co-occurring conditions, e.g. intellectual disability,</td>
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<td>Confidence in the MOA of the investigational drug</td>
<td>Argue the link between the investigational drug’s MOA to the underlying pathophysiology</td>
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<td>Provide data from cell based and/or animal-based models</td>
</tr>
<tr>
<td>Study duration</td>
<td>Treatment duration should be sufficient to observe a benefit, i.e. at least 12 weeks</td>
</tr>
<tr>
<td>Dose selection</td>
<td>Must be shown to be safe and well tolerated in phase 1 adult studies</td>
</tr>
<tr>
<td></td>
<td>If a pharmacologically active dose is identified in phase 1, an age equivalent dose for paediatrics needs to be determined to provide equivalent exposure</td>
</tr>
<tr>
<td></td>
<td>The dose should be sufficient to deliver a treatment effect</td>
</tr>
<tr>
<td></td>
<td>Endpoints should demonstrate a treatment effect on at least one core symptom which should be supported by a positive effect on functioning</td>
</tr>
<tr>
<td></td>
<td>COA rated by observers (e.g. parents) or clinicians which assess core concepts such as social communication and restricted, repetitive (continued on next column)</td>
</tr>
<tr>
<td>Clinical endpoints</td>
<td>Statistical considerations</td>
</tr>
<tr>
<td></td>
<td>Sample size and study power should be considered carefully and may be based on estimates on the ‘minimally clinically important difference’ derived from historical data, or psychometric properties of the primary endpoint</td>
</tr>
<tr>
<td></td>
<td>Set up an IMC or iDMC, guided by a charter</td>
</tr>
<tr>
<td></td>
<td>Ensure dedicated safety monitoring during study conduct</td>
</tr>
</tbody>
</table>

The unmet medical need in ASD remains high. Therefore, continued clinical research in this area needs to be encouraged. ASD generally manifests in early childhood and continues through adolescence and adulthood. Non-pharmacological interventions early in life generally lead to better long-term outcomes. It is expected that the same would apply for pharmacological interventions. Therefore, initiation of clinical trials in the paediatric population early in pharmaceutical development may be essential for signal detection.

In this White Paper we have consolidated various recommendations from various guidelines, CHMP and FDA advice from multiple programmes to aid industry and academic sponsors in the design of clinical trial protocols for first in paediatric ASD intervention studies.

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CRediT authorship contribution statement

Lindsay M. Ham: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. Hannah Staunton: Formal analysis, Writing – original draft, Writing – review & editing. Jan Michael Schulz: Formal analysis, Writing – original draft, Writing – review & editing. Julian Tillmann: Writing – review & editing. Dietmar Volz: Formal analysis, Writing – original draft, Writing – review & editing. Lorraine Murtagh: Writing – review & editing. Christopher Chatham: Funding acquisition, Writing – review & editing. Eoin C. O’Connor: Formal analysis, Writing – original draft, Writing – review & editing. Philipp Schoenenberger: Formal analysis, Writing – original draft, Writing – review & editing. Stormy Chamberlain: Formal analysis, Writing – original draft, Writing – review & editing. Paul Wang: Writing – review & editing. Celso Arango: Writing – review & editing. Declan Murphy: Funding acquisition, Writing – review & editing.
Declarations of competing interest

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