ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

ASD Working Group – Clinical Trial Design

Clinical Trial Design Lit Review Topics	Volunteer
Clinical trials investigating co-occurring disorders or symptoms	Cristan Farmer; Dejan Stevanovic Review results received in word file
Co-morbidity/concomitant meds	Gahan Pandina; Islam Younis
Context of trial…other treatments at same time as drug, standardization	James McCracken
Data in children below 5 years of age	Phil Chappell; Tiffany Farchione
Duration of observation	Juan Carlos Gomez; Paul Wang
How do you decide to take a new product into young children? What kind of data do you need to move the trial to children?	Phil Chappell; Tiffany Farchione
How to develop clinical centers for effective patients' recruitment	Dragana Burgarski-Kirola; Juan Carlos Gomez; James McCracken Slides received from Roche
How to integrate behavioral interventions	Gahan Pandina
Inclusion of individuals with intellectual disabilities (e.g. LEAP cohort)	Cristan Farmer; Dejan Stevanovic; Audrey Thurm Complete
Lessons learned from past clinical trials in ASD	Dragana Burgarski-Kirola; Eric Hollander Complete
Maintenance effects (may fall under duration of observation)	Paul Wang
Outcomes Measures	Oliver Howes
Placebo lead-in	Stefan Leucht; Jeremy Veenstra-Vanderweele
Subject selection/enrichment	Eric Hollander; Jeremy Veenstra-Vanderweele
Technology	Dragana Burgarski-Kirola; Gahan Pandina; Andrew Potter
Use of placebo and placebo effect in ASD trials (what is appropriate comparator?)	Stefan Leucht; Jeremy Veenstra-Vanderweele

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Topic 1- Inclusion/exclusion of individuals with intellectual disabilities (ID) in clinical trials

Psychol Med. 2011 Mar;41(3):619-27.
IQ in children with autism spectrum disorders: data from the Special Needs and Autism Project (SNAP).
Charman T, Pickles A, Simonoff E, Chandler S, Loucas T, Baird G.

- Comprehensive clinical assessments were conducted with 156 children aged 10-14 years [mean (s.d.)=11.7 (0.9)], seen as part of an epidemiological study (81 childhood autism, 75 other ASD). A sample weighting procedure enabled us to estimate characteristics of the total ASD population.
- Of the 75 children with ASD, **55%** had an intellectual disability (IQ<70) but only 16% had moderate to severe intellectual disability (IQ<50); 28% had average intelligence (115>IQ>85) but only 3% were of above average intelligence (IQ>115). There was some evidence for a clinically significant Performance/Verbal IQ (PIQ/VIQ) discrepancy but discrepant verbal versus performance skills were not associated with a particular pattern of symptoms, as has been reported previously. There was mixed evidence of a characteristic subtest profile: whereas some previously reported patterns were supported (e.g. poor Comprehension), others were not (e.g. no 'peak' in Block Design). Adaptive skills were significantly lower than IQ and were associated with severity of early social impairment and also IQ.
- In this epidemiological sample, ASD was less strongly associated with intellectual disability than traditionally held and there was only limited evidence of a distinctive IQ profile. Adaptive outcome was significantly impaired even for those children of average intelligence.
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Topic 1- Inclusion/exclusion of individuals with intellectual disabilities (ID) in clinical trials

Cristan Farmer; Audrey Thurm

Carlson, 2013 – Ethics of including people with ID in research, not specific for ASD, not addressing children
Williams & Moore, 2011 - Describes Universal Design of Research so that all people can be included as potential participants, not specific for ASD, not addressing children.
Spong & Bianchi, 2018 - Discusses impact on public health of exclusion of underrepresented populations, specifically ID and specifically as it pertains to pharmacokinetic data. Draws parallel to exclusion of children prior to Best Pharmaceuticals act of 2002. Presents review of active studies in ClinicalTrials.gov, finding explicit exclusion of ID for 12.4% of studies (most of remainder did not state). Authors call for clear justification in excluding members of these populations, not specific for ASD.
Osugo & Cooper - 2016 Formal review of multiple types of treatments for mental health conditions in adults with mild ID. Reports how few studies there are in mild ID, but how there are even fewer for those with more severe forms of ID. In fact, there were no RCTs of pharmacological interventions for individuals with mild intellectual disability.
Discusses the impact of exluding individuals with IQ between 70 and 85 from ADHD research
MacKenzie & Wonders, 2016 - Although specific to ADHD research, nearly every issue is applicable to ASD research. Excluding these individuals from research limits important understanding of how treatments might work (i.e., some data suggesting that stimulants work less well when IQ<85) and prevents us from understanding how ADHD coexists with other conditions because those individuals are excluded by way of IQ. Also that prevents us from understanding how ADHD and IQ influence each other. Raises issue of generalizeability; knowing that ADHD is associated with lower IQ, having a sample with average IQ is not representative.

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Topic 1- Inclusion/exclusion of individuals with intellectual disabilities (ID) in clinical trials

Unmet Needs

No clear policy recommendations on the appropriateness of including individuals with ID in clinical trials
No clear data on mild vs severe ID
No ASD data on experience of individuals with ID and ASD in a clinical trial setting
No normative data on outcome instrumentsù

Means to address unmet needs

EU-AIMS Leap Cohort enrols people with ASD and mild intellectual disabilities (as defined by an IQ below 70 ± 5 and low adaptive behaviour). Availability of results?

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Topic 2- Lessons learned from past clinical trials in ASD

Dragana Burgarski-Kirola; Eric Hollander

Hollander et al., 2012 - 37 randomized, fluoxetine treatment, compared to placebo, resulted in significantly greater improvement in repetitive behaviors, according to both the Yale-Brown compulsion subscale and CGI rating of obsessive-compulsive symptoms, as well as on the CGI overall improvement rating
Hollander et al., 2005 - 23/39 participants had intellectual disability
Liquid fluoxetine better than placebo in treating repetitive behaviour (CY BOCS compulsion score)
King et al, 2009 - Citalopram was not superior to placebo in this sample of children with ASDs. Neither the rate of positive global response to citalopram treatment, nor the dimensional scores of repetitive behavior on the blinded clinician–rated CYBOCS-PDD, nor the parent-rated Repetitive Behavior Scale–Revised scores suggested any difference between groups. Although a difference emerged between treatment groups on the Irritability subscale score of the Aberrant Behavior Checklist–Community version, this difference does not seem to be clinically meaningful, and absolute end point values were equivalent. Placebo response rate of 34.2% consistent with other studies
King et al, 2013 - Several baseline predictors of response were identified (disruptive behavior, autism/mood, and caregiver strain) that significantly predicted response at week 12. Specifically, participants in the placebo group were significantly less likely than participants in the citalopram group to respond at week 12 if they entered the study more symptomatic on each of the 3 composite measures, and they were at least 2 times less likely to be responders.

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Topic 2- Lessons learned from past clinical trials in ASD

Lessons learned from Fragile X studies

Box 2 | Conclusions from mGluR5 antagonist and $GABA_B$ agonist trials

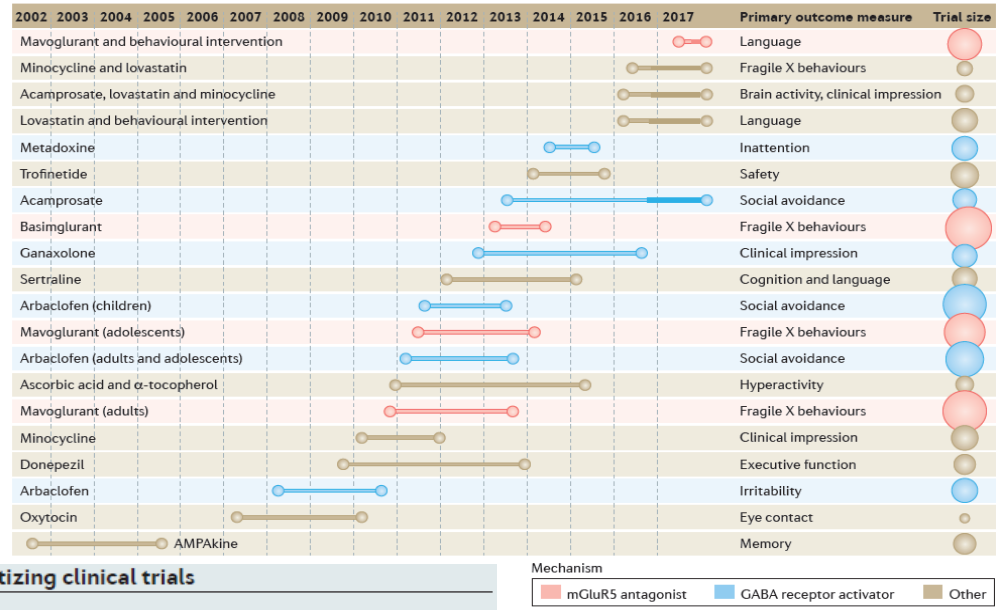
Basimglurant and mavoglurant (metabotropic glutamate receptor 5 (mGluR5) inhibitors) do not modulate behaviour within 3 months of the treatment period; however, arbaclofen (a $GABA_B$ agonist), which seemed to address behaviour, showed trends of efficacy in children in an analysis of the primary and secondary trial outcomes, without invoking a post-hoc analysis.

- The trials with mGluR5 inhibitors and $GABA_B$ agonists were sufficiently long to measure behavioural changes related to potential symptomatic effects of the drugs. Indeed, clinically active drugs in autism and other psychiatric conditions show efficacy for behavioural symptoms in adults, adolescents and children at treatment intervals shorter than 3 months (typically 4 weeks or less).
- The broad age range (12–40 years) should have enabled the detection of age-related therapeutic benefits, and age did not co-vary with response to mavoglurant in patients with fragile X syndrome (FXS) aged 12 years and older in these studies[69]. Of note, many psychotropic medications effective in adults also show some efficacy in adolescent patients. However, these medications, unlike arbaclofen, are largely targeted at behavioural support and not the underlying disease. In the arbaclofen studies, a possible signal of efficacy was seen in children aged 5–11 years, but not in adults and adolescents, suggesting the possibility that treatment needs to commence at younger ages to demonstrate disease modification.
- Enrolment of more than 100 participants was required to reach unequivocal negative findings, which calls into question the utility of smaller trials in neurodevelopmental disorders (NDDs), as these trials almost invariably identify significant improvement in one of the multiple post-hoc exploratory analyses. The additional burden of dose finding drastically decreases the power of these studies and should be taken into account.

The methodology and design of the trials highlighted key issues.

- Windows of plasticity: very young patients were not included in the studies reviewed above. Plasticity is expected to be much higher in young children, and this may be the only group in which effects of a disease-modifying agent targeting cognition and development can be seen in the time period assessable by a placebo-controlled trial. Trials in adults and adolescents may be able to detect drug effects only if there is a direct effect on a specific area of behaviour.
- Measuring change: primary outcome measures were mostly questionnaires performed by caregivers and showed large placebo response. Objective measures of core phenotypes rather than secondary behaviours, such as direct assessments of cognition and language that are less subject to placebo response and have less inherent variability than caregiver-rated scales, need to be implemented in future trials.
- Measuring disease modification in NDDs: efforts may need to be redirected towards the implementation of longer trials in younger children accompanied by learning interventions measuring cognitive and developmental outcomes

Therefore, it cannot be excluded that mGluR5 antagonists might show improvement of the developmental trajectory and cognition when tested in very young subjects with longer treatment duration.



Box 4 | A framework for prioritizing clinical trials

To increase the quality of trials in fragile X syndrome (FXS) and maintain patient safety and community engagement, we propose criteria to prioritize new clinical trials based in part on previous publications[106].

- Target mechanism: evidence supporting target selection is one of the most challenging aspects. Preclinical data should be reviewed using the guidelines detailed in BOX 3. Efforts to develop biomarkers should be prioritized.
- Tissue and target exposure: an in-depth understanding of pharmacokinetics and pharmacodynamics is required.
- Safety and risk–benefit consideration: the safety and toxicological data set needs to support the use of investigational drugs for the targeted age range and treatment duration. Juvenile toxicology studies are a mandatory requirement for paediatric clinical studies to assess the potential of unique toxic effects in younger age groups.
- Trial design: given the high placebo response rate, objective performance-based outcome measures should be used, and open-label trials should be avoided except in particular instances (such as safety data or to establish the validity of an important biomarker).
- Statistical power: a single well-powered study is more useful than several smaller inconclusive efforts. Exploratory outcome measures are often important aspects of phase II trials and require large sample sizes or replication. Power will represent a serious logistical and financial hurdle for future trials in FXS and other 'genetically defined' neurodevelopmental disorders. Adaptive multistage Bayesian Design trials are strategies that may be used in the context of dose findings, but clear end points or biomarkers are required to implement phase II and III trials. *n*-of-1 trials are a promising method that will also require objective and valid measures that can be extensively repeated.

Berry-Kravis et al

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Topic 2- Lessons learned from past clinical trials in ASD

Unmet needs after review of lessons learned

- Need to establish appropriate amount of evidence before start of confirmatory program
- Need to establish optimal size of clinical trial population (2 small or one large study?)
- Optimal age range to detect age differences in response to treatment (2 trials in age groups or subgroup analyses?)
- Need to establish optimal trial duration to measure behavioral changes

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Topic 2- Lessons learned from past clinical trials in ASD

Lesson learned from oxytocin trials Alvares et al., 2017

•Only a small number of individuals with ASD have actually been reported being administered oxytocin or placebo (a total of 390 individuals with ASD across 21 publications, ranging from randomized trials to open-label investigations and case studies), with very little investigation in females and almost all studies exclusively recruiting higher functioning individuals.

•The search for **objective biomarkers** to quantify changes in response after oxytocin administration need to be complemented by measures of clinical efficacy.

•Lack of satisfactory methods for measuring oxytocin to characterize the **dose-response** curve

•Low recruitment rate of **females** in ASD clinical trials places significant limitations on the generalizability

•An additional limiting factor is the exclusion of individuals with a range of behavioral and cognitive profiles.

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Topic 3- How to develop clinical centers for effective patients' recruitment

Examples from other disease areas

- Craig H. Mallinckrodt et al., 2010 - Signal detection and placebo response in **schizophrenia**: parallels with depression
- A Masi - Predictors of placebo response in pharmacological and dietary supplement treatment trials in pediatric autism spectrum disorder: a meta-analysis
- Michael J. Fox Foundation (MJFF) Clinical Trial Strategies team- clinical trials recruitment best practices manual (**Parkinson's disease**)
- Katja Weimer et al, 2015 - Placebo effects in psychiatry: mediators and moderators
- Adwoa Hughes-Morley et al., Factors affecting recruitment into **depression** trials: Systematic review, meta-synthesis and conceptual framework

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Topic 4- Clinical trials investigating co-occurring disorders or symptoms

Review and conclusions

•A total of 45 studies remained after applying these inclusion/exclusion criteria. Seventeen of these studies did not explicitly recruit for the comorbidities; instead, they just allowed them (or appeared to, as comorbidities were not included in exclusion criteria). Among the 28 studies which included comorbidities as an inclusion criterion, 16 included behavior problems like irritability, aggression, and tantrums, and nine included ADHD (or ADHD symptoms). None of the included studies recruited specifically for any other disorder, such as anxiety or mood.

•Only one of the studies recruited specifically for ID (plus behavior disorder); another study initially planned to require ID but later opened recruitment to non-ID. Most studies allowed (or did not explicitly exclude) the full range of intellectual disability (or IQ), but 11 studies excluded participants with IQ below the mild range of impairment. Other studies employed a mental age cutoff (e.g., 18 months).

•None of the reviewed study explicitly reported modifications to the protocol used to make possible the inclusion of individuals with comorbidities. Thus, the summary of our review of clinical trials is that there are too few available studies of individuals with ASD and ID or another comorbidity to guide recommendations.

•Finally, we also provide some references regarding the inclusion of underserved populations in clinical research. While these are not specific to ASD, they do provide data-based estimates of rates of inclusion in medical research, as well as discussion of the ethical implications of excluding individuals with ID or other comorbidities from research.

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Post 11 Sept. call conclusions:

Issues to put forward to Marina del Rey:
Maintenance of effect
Duration of the trial
Duration of observation to observe effect on different outcome measure
Fast effect on symptoms like anxiety vs persistent effect on dimensions like social skills
Maintenance vs disease modification regulatory/clinical perspective
Placebo effect - predictors moderators – placebo lead-ins
Steps necessary to move the trial into children as young as 2/3 years

Issues covered by Literature Review:
Inclusion of IDs
Inclusion of comorbidities
Lessons learned from past clinical trials
How to develop clinical trials centers for effective recruitment
Use of technology (partially covered and overlapping with biomarkers digital phenotypes and digital outcomes)
Trials in children regulatory perspective