Lessons Learned from a Review of Clinical Trial Designs in Autism Spectrum Disorders and Fragile X Syndrome

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Conflicts of Interest

Source	Consultant (past or present)	Stock or Equity Interest	Speakers' Bureau	Research Support (past or present)
Bristol-Myers Squibb				X
Roche	X			X
Seaside Therapeutics	X			X
Novartis	X			X
Confluence Pharmaceuticals	X	X		
Dept of Defense				X
AACAP				X
FRAXA Research Foundation				X
Indiana CTSI				X
Indiana DDRS	X			X
Simons Research Foundation				X
Autism Speaks				X
Cincinnati Children's Hospital Research Foundation				X

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Lessons Learned

- Concomitant Medications
- Target of Treatment
- Building Research Capacity in the Field
- The Bridge from Fragile X to Autism
- Impact of Patient Age
- Issues with Placebo
- Is all good press really good for studies?

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Concomitant Medications

- What we know?
  - Atypical antipsychotics have large effect sizes targeting irritability
  - Atypical antipsychotic use is associated with at least a trend towards symptomatic improvement in other domains
    - Social withdrawal
    - Hyperactivity
    - Repetitive Behavior

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Concomitant Medication

- Impact of concomitant drug exclusion
  - Clearly biased sample population to highest functioning/most minimally affected minority of persons with ASD or FXS
    - May, though, be subjects most able to tolerate early Phase studies with any PK draws/intense study requirements
  - Helps “preserve the pathology”, ie: more significant room to move outcome measures
    - Boosts potential drug effect sizes almost regardless of target symptom

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Concomitant Medications

- If concomitant drugs prohibited in initial study, consider not giving up on the drug if results are negative
  - Use initial study in those most minimally affected/ maximally tolerant of study procedures to inform dosing/tolerability, with potential for signal informing choice of future outcome measures
  - Other alternative is prohibit con meds AND *wait* for significantly impaired persons on no meds/willing to come off medications
    - Likely much easier 10+ years ago

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Concomitant Medications

- Middle Ground Approach
  - Consider prohibiting atypical antipsychotics
    - Drug class most likely to have significant across the board effect on various target symptoms
  - Allow other medications that families may be attached to
    - Drugs with limited, if any, evidence base: Buspirone, oxcarbazepine, naltrexone
    - Drugs with more/growing evidence base, but narrow target symptoms: atomoxetine, alpha-2 agonists, stimulants

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Concomitant Medications

- Fragile X Syndrome
  - The field has generally accepted con med use in RCTs
  - Driven by rarity of disorder/fear of slow recruitment
    - *Could* contribute to lack of findings on primary outcome measures utilized in RCTs in recent years

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Target of Treatment

- If first RCT, use broad range of outcome measures
  - Amazing how some first RCTs fail to use gold standard measures likes the Aberrant Behavior Checklist (ABC)
- Consider using a cutoff for study entry based on theoretical target of treatment
  - Example: one standard deviation above the mean on a specific ABC subscale
    - Otherwise, potentially have no where to move on a measure

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Target of Treatment

- *Consider* initial open-label study prior to Phase II to better define target of treatment/weed out non-performing drug(s)
  - Expect a high response rate
    - If >2/3 do not respond in open-label pilot study, consider moving on with something else
  - Utilize experienced ASD clinical researchers in potential OL study to ensure experience in teasing out intricacies of treatment effect
    - Avoid the "everything is better phenomena"

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Building Research Capacity in the Field

- The more rare the disorder, the more capacity needs to be built
  - ASD field now has a history of multiple federally-funded clinical trials research groups/units
  - Fragile X Syndrome lacked such capacity when targeted trials were initiated
    - Well meaning clinical centers thrust into targeted drug research is a recipe for the following:
      - Doing anything to get a subject in a trial (CGI-S scores)
      - Trying to read side effects and predict treatment assignment in an effort to “help out the study”

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Building Research Capacity in the Field

- NIH showed an interest in building Fragile X Syndrome multi-site clinical trial capacity
  - But to date has not funded multi-site trials or multi-site outcome measure development programs
  - Therefore up to industry to train sites
    - More rare the disorder/subgroup of focus in ASD trials, the more sites are needed
      - More sites needed, means less site experience and the pitfalls of lack of experience
      - Need to speak openly at investigator meetings/calls that deviating on entry criteria or predicting what a patient is getting and sharing with the family/research team does not help anyone
      - Note if you get lower response rates at more experienced sites!!

The Bridge from Fragile X to Autism

- Fragile X is different
  - Autism by DSM IV or V definition does occur in some persons with FXS, but “FXS autism” is likely unique
    - Clinically autism in FXS often looks different than idiopathic autism
  - Though relatively homogenous compared to autism, the FXS presentation is heterogeneous
    - Subgroup findings in recent FXS RCTs
  - FMRP is a single protein, but a single protein with wide-ranging effects

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The Bridge from Fragile X to Autism

- Most useful to think about links via specific target symptoms
  - For example, a drug found in FXS study to limit irritability may help irritability in some persons with idiopathic autism
    - Example of atypical antipsychotics
      - Could have studied atypicals in either disorder first and extrapolated findings to the other disorder
  - Avoid overly thinking about FXS “disease modifying” agents “modifying disease” in autism
    - Different pathophysiology with overlapping symptoms

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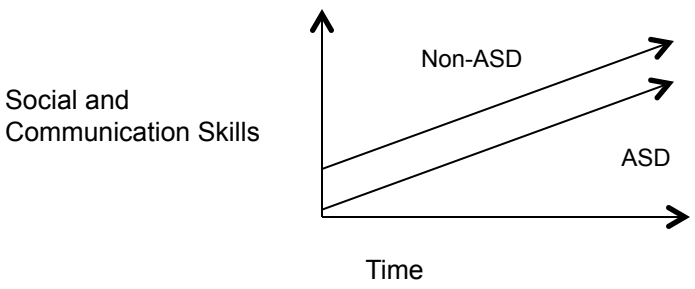
Impact of Patient Age

- Developmental Disorders Present Differently Based Upon Developmental Stage
  - Difficult to assume drug impact on core social/ communication deficits in adults with autism (or even FXS) will provide a direct read out on drug effect in youth
  - In autism, social/communication skills may change
    - Throughout life new skills can be learned in ASD or FXS



Parallel Trajectories?
ASD social/communication skills are inherently a moving target

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Impact of Patient Age

- Presents concern with need to study many investigational agents first in adults
  - May miss “early window” when drugs could have the greatest effect
  - Adult animal data not convincing enough to warrant abandoning drug trials with a limited response in adult autism or FXS
    - What is optimal age to study?
      - Getting down to age 5 now
      - Hope some symptomatic change in childhood will support younger subject study

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Issues with Placebo

- Autism targeted treatment (social/communication) placebo response rate is about 33%
  - Much higher than irritability trials, but still lower/same as rates in depression/other disorders
- Higher placebo rate combined with lower effect sizes anticipated = large trials
  - Lower effect sizes may be due to:
    - Impact of concomitant meds
    - Heterogeneity of sample in “targeted” study versus homogeneity in symptomatic study
      - As many different causes of autism as # of patients
      - Compared to studies targeting unifying behavioral feature

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Issues with Placebo

- Considered designs:
  - Single-blind placebo lead-in to remove earliest placebo responders
    - Followed by randomization
    - Removes families most driven to see success with anything

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Issues with Placebo

- Consider Novel Designs:
  - Placebo-controlled withdrawal
    - Focus on potential drug responders
    - Good for study recruitment, especially if rescue is involved/available
      - Families like idea of addressing “how long does my child need the drug”
    - Potentially easier to accomplish in social/communication focused studies versus irritability focus
      - No known treatment, no knowledge of how long treatment is needed, potentially less risk with withdrawl

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Is all good press really good for studies?

- “Nutritional therapy may be key to stopping autism”
- “Parents Pleased With New Autism Treatment”
- “The First Drug that Could Ease Social Withdrawal in Autism”
- “New drugs, fresh hope for autism patients”
- “Special Report: New drugs, fresh hope for autism patients”

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Is good press really good for studies?

- Good PR brings in many families- when the families find you versus you find the family
  - Potentially more difficult to define entry criteria
    - May be more likely to "say anything" to get in study
      - Occasional trouble with ADI-R inclusion criteria
  - Sometimes very desperate and very, very hopeful
    - Risk of increasing placebo response rate even more

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Is good press really good for studies?

- Difficulty of study participation not considered
  - Participating in research sounds good in theory, but studies are burdensome for families
    - May be more likely to start a study, not see a quick "cure" and drop out versus respond to placebo
      - We see more families lost to follow-up in high profile projects
      - May be due to distance travelled

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Any questions?

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