Review Paper

Ethical Issues in Clinical Trials that involve Children with Autism Spectrum Disorders

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ABSTRACT

Autism spectrum disorders is one of the commonest developmental disabilities that is seen in clinical practice. There have been a number of new interventions that have been posited to be useful in the management of autism spectrum disorders. This has resulted in the need for sound clinical trials using these interventions in management of children with the condition. The present paper provides an overview of the various ethical issues that arise when conducting clinical trials in children with autism spectrum. Issues like informed consent, legally acceptable representative and safety have been discussed. The paper will serve as a primer for those working in the area and even undertaking clinical trials in this population.

Keywords: clinical trials, autism, autism spectrum disorders, ethical, children.

Introduction

Research on Autism spectrum disorders (ASD) have increased in the last 2 decades with the confluence of increased awareness of ASD globally and increased funding opportunities for conducting research on ASD [1-2]. This necessitates attention towards research ethics. Although pediatric bioethics is a well-established field, very little is written about ethics of research in children and adolescents with disability [3]. Given the history of research ethics, guidelines were laid due to the unethical research conducted on children with intellectual disability [4]. Efforts to enhance research regulation and protect children against exploitation in research culminated in the development of guidelines such as the World Medical Association's Declaration of Helsinki [5]. The thought of potential abuse, confusion over consent, lack of capacity to consent, fear of litigation, difficulty in accessing this population and limited profit for pharmacological companies had led to a decline in research among children and adolescent with developmental disorders [4]. Exclusion of children with disability from research has led to sub-standard treatment for them and unequal access to the benefits of research. In this era, accessing and inclusion, as opposed to protection, are becoming dominant themes [3]. In this article too we will be discussing about ethical issues faced by researchers at various stages while conducting research in children with autism spectrum disorders.

Current State of Clinical Trials in Autism Spectrum Disorders

Most knowledge on treatment guidelines and recommendations on autism are typically based from short-term interventional studies. There is a lacuna of knowledge about key questions, such as what interventions and support strategies are effective for which age group, which interventions can lead to a change beyond their proximal outcomes, interventions should be given for how long with what expected outcomes and for what cost. The genetic and neurobiological research are still in a stage of infancy in finding a biological ideal treatment or cure for autism, which has led to a huge gap between clinical challenges and their solutions [2]. Medications for the core symptoms of autism are yet to be approved by any regulatory agencies [2,3,6]. Clinical trials in ASD have produced several supportive pharmacological treatments for the associated symptoms with not much evidence to treat pharmacologically the core symptoms [4]. Atypical antipsychotics such as risperidone and aripiprazole, have been approved by United States (US) Food and Drug Administration (FDA) for the treatment of irritability associated with ASD and Risperidone for the same purpose has been approved by the European Medicines Agency [2,6]. The use of Methylphenidate, Atomoxetine and Clonidine for the treatment of ADHD symptoms in children with ASD have been supported by clinical trials. Melatonin has shown considerable effectiveness in treatment of insomnia, particularly for improving sleep onset. Several agents such as selective Serotonin reuptake inhibitors, dopamine antagonists, glutamergic agents (Memantine, D-cycloserine, Acamprosate), GABAergic agents (Arbaclofen) and neuropeptides (Oxyctocin, Vasopressin) have shown effectiveness in core symptoms of autism in small studies, unfortunately the effect couldn't be replicated in medium sized randomized controlled trials (RCT) studies [6].

Nonpharmacological interventions for stereotyped and repetitive behaviors in ASD children that have been used are behavioral, massage and music therapies, audiovisual stimulations and virtual reality, family-implemented treatment for behavioral inflexibility with treatment approach, animal or pet therapies, etc. The early intensive behavioral interventions such as applied behavior analysis is used to improve language, cognitive ability and adaptive skills. The evidence in support for such interventions is weak and same effects have not been replicated in large studies [2, 7-9].

Informed Consent in Autism Spectrum Disorders – ethical issues

Obtaining informed and voluntary consent or assent is a necessary part of all research. The purpose is to ensure that the participants understand the aim of the study, the associated risks and the expected outcomes [10]. This becomes paramount in clinical trials as these are interventional in nature and consent becomes an ongoing process in the various time frames of the intervention.

When it comes to clinical trials for individuals with autism, there are various factors which may complicate the process: majority of the participants are children, who legally cannot provide consent, or adults who are unable to give consent due to their limited capacity, as determined by the researchers.

Although parents or caregivers of individuals with ASD are likely to be the family members who initially show interest in the study, it is important to ensure they do not provide consent on behalf of other members of their family. Individuals with ASD and children may be particularly vulnerable to having their consent provided for them. Similarly, although parental/care givers consent is generally the primary requirement needed for children to be involved in research, this should not replace obtaining assent from the individuals with ASD and children themselves [10].

Developmentally appropriate information and communication techniques are required for meaningful consent and assent. They must be presented in an accessible manner ensuring better understanding of the entire process (e.g., simplified language, video, audio-visual aids) [3,11]. Adequate time needs to be provided and consider repeating the responses of the individual to ensure the clarity of the process [11-12].

Accessible communication strategies such as assessment by a specialized communication team (e.g., speech-language pathologists and occupational therapists) and the use of augmentative or alternative communication devices or techniques may be required depending on the child's age, level of disability and communicative competencies [11-13].

Collaborative and child- and family-centered consent is an important strategy for optimizing the consent process. Here, the parents, caregiver and child are consented or assented together.

Adolescents with ASD having limited communicative competence, may have an emerging capacity to consent. Therefore, they would require provisions for capacity assessment to provide consent [3].

Often parents who are being approached for a clinical trial are under the assumption that if a particular molecule is being researched, it must be effective and hence consent with that frame of mind. The desperation to have some kind of help for their child may drive them to participate, even in stem cell research trials, often discounting the risks involved, as it seems their only ray of hope. Parents often have very limited understanding of the research process and hence expecting them to make an 'informed' choice is imprudent [1].

Legally acceptable representative (LAR) – ethical issues in ASD

The legalities that govern research involving adults who lack capacity to consent varies across countries, and at times even within legal jurisdictions in the same country. They also vary depending on the nature of the clinical trial. These guidelines lay down criteria such as proxy decision maker, the level of risk permitted, level of intervention and the amount of information regarding the trial which can be made available to the individual who lacks capacity to consent [14-15].

For adults who lack the capacity to consent to research, a surrogate decision-maker often acts as a legal representative. This individual is involved in the decision of participation in the trial. The legal frameworks governing who can act as a legal representative also vary across countries [14]. Many a times, the participants (legal representatives) are provided with a renumeration to participate in the study, which can highly influence their decision to do so.

Few countries have given a list of individuals who can give a proxy consent for the individual: guardian, spouse, adult son or daughter, parent, adult sibling, adult grandchild or other close relative, close friend, and guardian of estate. It has been suggested that medical professionals, providers, or employees of a provider should not be appointed as legal representatives, due to conflicts of interest [15].

Interventional pharmacological and non-pharmacological trials in ASD – dangers and ethical issues

Pharmacological interventions have shown evidence in reducing irritability and comorbid psychiatric symptoms, whereas non-pharmacological interventions such as Applied Behavioral analysis (ABA) have shown significant reduction in the core symptoms in ASD with milder severity, higher intellectual functioning and early age of starting the intervention [2,6,16]. There could be certain dangers with pharmacological interventions such as side effects of a particular drug and assessing the cost and benefit of polypharmacy [17]. Few studies on ABA show that there is a point of diminished returns with too high treatment intensity [16]. There have been limited data on age at which non-pharmacological interventions have to be started. Documentation and reporting of potential for negative side effects while using punishment, negative reinforcement in behavior therapy are limited [16]. The data on eclectic treatment is limited. When individuals undergoing such eclectic treatment approach participate in a study, there is no clearcut understanding about which therapy is being beneficial and which one is harmful and has no benefit. The issue in such an approach also arises that the beneficial treatment may not be received by the client at a high intensity when compared to a non-beneficial treatment [16].

Vulnerability of parents of children with ASD and clinical trials

As we know, there have been fewer interventions to modify the behaviors of ASD and they take longer time to achieve such behavioral changes, parents are desperate to find a cure that works instantly. This desperate need leads them to take measures such as participate in a research project, without regard to its efficacy and clinical safety [1]. With a limited understanding of ASD and research on it, it is difficult for parents of ASD to provide consent for any research. Due to the ubiquity of therapeutic misconceptions, parents typically believe that an intervention being researched means it is known to be effective.

The research conducted on ASD families recruited from schools reveals that they are constantly afraid of being expelled from school and avoid inquiring about the research. The consent provided by parents of ASD in research for a new intervention could have been due to coercion or enrolment without the knowledge of the parents such as a random school assignment or blood sample drawn for some other test used [1].
It's the duty of researchers to provide parents with sufficient time to consider the elements of consent, the known risks and possible benefits of the promising, but unproven therapy, are understood. The parents must be given the opportunity and facility to consult with other family members and their child with similar situation to the extent possible. Also, parents have to be explained about the meaning and likelihood of randomization into a non-medicinal treatment arm [3].

Stem cell use in ASD – ethical issues and studies
Studies portraying that Stem cell interventions (SCI) that have provided benefits are usually unblinded, nonrandomized, uncontrolled studies and preliminary in nature. There have been no convincing evidence of randomized controlled trials showing safety and efficacy of Stem cell therapies for ASD. Stem cell therapies for ASD have not been licensed and stem cell interventions are not part of the evidence-based standard of care for persons with ASD [18].
The studies on stem cell therapies are mainly focusing on the usage of iPSC (induced pluripotent stem cells) and mesenchymal stem cells (MSCs) in treatment of ASD. Due to the genomic instability of iPSCs, even improved protocols for their differentiation, do not guarantee safe clinical application and may result in generation of tumors. Similar unwanted differentiation is seen in the transplanted MSCs due to their potential to suppress anti-tumor immune response and generate new blood vessels that may promote tumor growth and metastasis [19-20].
Many parents pursue stem cell therapies for their children with ASD despite the lack of robust safety and efficacy supporting it. The costs are typically not covered by health insurance and push families to engage in crowdfunding to pay for such expensive procedures. Pay to participate or patient funded studies or other funded studies contain significant scientific limitations and undisclosed forms of bias that questions their credibility. Such studies also may not document the adverse effects. When a reward is involved for participation, there can be risk of placebo amplification. Ethical concerns should focus on SCI's marketing claims that can influence client's decision in participating in the study as well as information provided about beneficial, adverse and neutral effect from the interventions [20].

Compliance and Adherence issues in ASD clinical trials – ethical issues
According to Gudjonsson, compliance is the tendency of an individual to go along with propositions or carry out the requests or demands of others [21]. Chandler and others found that autistic individuals had a significantly higher tendency to comply with the requests of others when compared to non-autistic individuals [22]. Other studies have shown that both children and adults are not suggestible but are compliant [23-26]. The majority of autistic individuals participate in research because they want to contribute to research, improve the lives of autistic individuals, learn more about themselves, feel accepted and generally wanting to be helpful and supportive [22, 27-28]. Compliance is a major factor to success of most research that include autistic individuals. The important ethical issue for researchers is regarding the requests they make to autistic participants of not over-burdening them to continue taking part beyond what is reasonable. Autistic reasoning and perceptions of fairness should be examined more closely in future research in the context of compliance to research and other types of requests [22].
Certain non-pharmacological research trials involve interventions provided by the therapists and or by parents. The adherence to specific protocols and specific methods in research is difficult to monitor. Adherence at different level that needs to be monitored are trainer adherence while training therapists; therapist adherence while teaching parents; parent adherence while working with their children. The monitoring of intervention adherence of trainers and therapists can be conducted through direct supervision or video assisted supervision [29]. The videotaping in one of the studies conducted showed they were blind as to whether videotaping was done for the purpose

of monitoring child's behavior or fidelity of the therapists [30]. The ease of taking consent from a therapist to monitor their intervention adherence is feasible when compared to the parents. Parents adherence to intervention poses certain difficulties such as consent for monitoring their adherence, timing of session (distributed throughout the day) and location (may not have fixed location at home). Studies have studies have assessed parental adherence through daily reporting of hours of delivery of intervention, knowledge test, self-competent assessments, change in parent child interactions, video and direct observations by a supervisor [29].

Ethical Issues for the future in ASD

A number of ethical issues arise for the future in clinical trials in children with ASD. The advent of robotics and artificial intelligence has opened up newer paradigms in the management of children with ASD but also pose new ethical challenges. How will one have clinical trials using robotic interventions which may not be totally in our control as they are programmed. The advent of brain-based interventions like neuromodulation and radiology guided transcranial magnetic stimulation as well as deep brain stimulation which are invasive procedures has opened up new issues for clinical trials in this area. ASD is a biologically heterogenous disorder. This may result in marked heterogeneity in the clinical responses to interventions as the response may vary child to child and this could also skew the results of clinical trials. There is a need for rigorous scrutiny of methodology of clinical trials with independent observers for these trials so that the human rights and vulnerability of families and children with ASD are not exploited.

Conclusions

Thus, there are a large number of ethical issues that arise in clinical trials with children that have ASD. There is a need for ethics committees to be cognizant of the various issues and the need for interdisciplinary evaluation and collaboration in these trials and the need for stringent observation and that no violation of ethical issues happen. There will be a need for committees to be formed that will develop guidelines for conducting clinical trials in children with ASD which will serve as a general guideline for the same.

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