angelman
SYNDROME FOUNDATION






Clinical Trial Excellence Resource

An Overview of Angelman Syndrome (AS), The Angelman Syndrome Foundation and The Effective Management of Clinical Trials in AS

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Authorship & Acknowledgements

This document was prepared by the Angelman Syndrome Foundation with the collaboration of Deirdre Neenan-Smith and Rebecca Wood.

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List Of Abbreviations

ADR: Adverse Drug Reaction

AE: Adverse Event

AFO: Ankle Foot Orthotic

AS: Angelman Syndrome

ASF: Angelman Syndrome Foundation

ASO: Antisense Oligonucleotide

CE: Clinical Evaluators

CIOMS: Council for International Organizations of Medical Sciences

CNS: Central Nervous System

CRC: Clinical Research Coordinator

CRF: Case Report Form

CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats

CVS: Chronic Villus Sampling

DNA: Deoxyribose Nucleic Acid

Dup15q: Chromosome 15q11.2-q13.1 Duplication Syndrome

EMG: Electromyography

FDA: Food and Drug Administration

FISH: Fluorescence In Situ Hybridization

GCP: Good Clinical Practice

HHS: United States Department of Health and Human Services

HINE: Hammersmith Infant Neurological Examination

IC: Industry Collaboration

IC Deletion/Defect: Imprinting Center Deletion/Defect

ICF: Informed Consent Form

IEC: Independent Ethics Committee

IRB: Institutional Review Board

IRDiRC: International Rare Disease Research Consortium

IT: Intrathecal

IV: Intravenous

LADDER: Linking Angelman And Dup15q Data for Expanded Research

M: Mean

MAGEC: MAGnetic Expansion Control

MFM: Motor Function Measure

MRCT: Multi-Regional Clinical Trials

NIH: National Institute of Health

NV: Noninvasive Ventilation

OT: Occupational Therapy

patUPD: Paternal Uniparental Disomy

PCP: Primary Care Physician

PI: Principal Investigators

PNCR: Pediatric Neuromuscular Clinical Research Network

RUSP: Recommended Uniform Screening Panel

SAE: Serious Adverse Events

SMN: Survival Motor Neuron

SC: Study Coordinator

SOC: Standard Of Care

SOP: Standard Operating Procedure

TIMPSI/TIMP: Test for Infant Motor Performance

UBE3A: Ubiquitin-protein Ligase E3A

US: United States

WHO: World Health Organization

WMA: World Medical Association

Introduction

Since funding its first clinical trial in 1996, Angelman Syndrome Foundation (ASF)-funded research has continued to lay the foundation for future discovery. ASF has invested more than $17 million in research to date, supporting projects worldwide in the quest to find treatments and ultimately a cure.

ASF funds research that falls into three categories:

1. High-risk, high-reward strategies to find cure, including topoisomerase inhibitors, ASOs, gene therapy and CRISPR
2. Clinical studies to alleviate symptoms and improve quality of life
3. Studies that help us learn about UBE3A and what it does in the brain.

ASF focuses heavily on pilot funding. Essentially, ASF uses a small amount of money to test drive an idea. If the test drive looks good, the researcher is then able to ask larger agencies, like the National Institutes of Health, Simons Foundation and other pharmaceutical companies to provide more funding to expand the project. Every pivotal idea started with pilot funding.

When ASF chooses projects to fund, they do so with the knowledge that incremental studies enable the next big leaps. The $17 million in research that ASF has funded has led to others contributing an additional +$200 million to the cause.

Treatments resulting from ASF's investment in research have helped individuals with AS learn to walk, communicate and live better lives today. But ASF is not stopping now. The Angelman Syndrome Foundation and their partners believe AS can be cured, so that those patients and their support system can lead better lives tomorrow.

To better meet the needs of trial sponsors and the AS patient community in the context of this evolving landscape, ASF has launched a Clinical Trial Preparedness Resource in order to support clinical trial site readiness throughout the United States. These activities have been undertaken with the understanding that while clinical trials in general are extensive undertakings requiring significant preparation, time, and expense; clinical trials in AS present unique challenges.

In AS trials, it is important to consider:

- the evolving natural history of Angelman syndrome as the standard of care evolves and approved therapies become available.
- the multiple outcome measures that can be used to evaluate clinically meaningful changes, depending on AS type; and
- the day-to-day burden that AS places on patients and families, which can make their participation in clinical trials especially challenging.

This resource is part of ASF's broader efforts to optimize site preparedness for AS clinical trials. It was developed to address research sites preparing for and conducting clinical trials, as well as specific issues that may be likely to arise within clinical trials in AS, and has four major sections:

1. "About Angelman Syndrome" which provides information on AS as a disease, its diagnosis, classification, and disease management.
2. "Angelman Syndrome Foundation" which highlights the ASF funded research, clinical centers of excellence, LADDER and helpful information and resources.
3. "Conducting Clinical Trials in Angelman Syndrome," which delves into trial preparation and conduct, with discussion of AS-specific considerations.
4. "Appendices," with key terms and additional resources, including useful links and information to assist with protocol adherence that have been prepared by other organizations and individuals.

Sites are encouraged to view this resource as a guide, and one of many tools that can be helpful - noting that guidance from clinical trial sponsors, institutional review boards (IRBs), and regulatory authorities should always take precedence when planning for, conducting, and closing trials.

Part 1:
About Angelman Syndrome

About Angelman Syndrome

Named after Dr. Harry Angelman, an English physician who discovered the syndrome, Angelman syndrome (AS) is a rare neuro-genetic disorder. It occurs in one in 15,000 live births. Angelman syndrome is often misdiagnosed as cerebral palsy or autism due to lack of awareness.

Characteristic features of this condition include delayed development, intellectual disability, severe speech impairment, and problems with movement and balance (ataxia). Most affected children also have recurrent seizures (epilepsy) and a small head size (microcephaly). Delayed development becomes noticeable by the age of 6 to 12 months, and other common signs and symptoms usually appear in early childhood. Children with Angelman syndrome typically have a happy, excitable demeanor with frequent smiling, laughter, and hand-flapping movements. Hyperactivity, a short attention span, and a fascination with water are common. Most affected children also have difficulty sleeping. Other features can include unusually fair skin with light-colored hair and an abnormal side-to-side curvature of the spine (scoliosis).

The life expectancy of people with this condition appears to be nearly normal. Individuals with Angelman syndrome will require life-long care. Because of its genetic relationship to autism and other disorders, many researchers believe that curing Angelman syndrome will lead to cures for similar disorders.

Prevalence of Angelman Syndrome

There appear to be no reported prevalence studies that have screened newborns to detect rates of AS. Population wide prevalence figures would need to take into consideration that longevity in AS is probably reduced (severe mental delay and seizure presence would be risk factors) but no actuarial or other data are available on life span shortening. Likewise, it is not known what percent of individuals with AS are undiagnosed, although this is expected to be significant. Accordingly, to estimate the number of people with AS living in the society, it would be inaccurate to divide any estimated AS prevalence figure into a total population number. Given this information, it appears that the prevalence of AS among children and young adults is between 1/10,000 and 1/20,000. It is suggested to use a 1/15,000 figure if a single figure is needed. For population projections, estimates using birth rates can be used. For example, if an area has a birth rate of about 200,000/year it would be estimated that about 13 babies would be born each year with AS.

Symptoms of Angelman Syndrome

Some symptoms can vary and be more severe than others, but in most children diagnosed with AS, the following are present:

- Developmental delays. These can vary from individual to individual, but common delays are: Infants (0-24 months): Inability to support one's head, pull oneself up to stand and delayed motor skills like crawling. Feeding issues due to problems sucking or swallowing. Young children: Delayed ability to walk and an unstable gait or balance issues.

- Seizures. Usually begin to occur between 18 months - 3 years old
- A happy demeanor. Frequent laughing, smiling and easily excitable
- Sleep problems. Abnormal sleep-wake cycles and diminished need for sleep
- Lack of speech. Infants display lack of cooing or babbling; young children usually use nonverbal methods of communication because conversational speech is either absent or limited to very few words.

What Causes Angelman Syndrome

Humans have 46 chromosomes inside every cell in their body. We receive 23 chromosomes from our mother and 23 from our father. Different genes are located in each chromosome. The Angelman syndrome gene, UBE3A, is located at chromosome 15.

Some genes on the chromosome are turned on or expressed, and others are turned off or silent. In typical humans, the UBE3A gene from our father is silent and the UBE3A gene from our mother helps our brain develop. However, in individuals with Angelman syndrome, there is a problem with the UBE3A gene from the mother and the brain cannot get the information it needs to develop and control speech, movement and learning. All this action in the chromosomes takes place during fetal development and thus is part of a person's genetic makeup.
When the UBE3A gene does not function normally, the individual has Angelman syndrome. Scientists around the world are studying the UBE3A gene and trying to find ways to turn on or unsilence the copy from the father.

Testing and Diagnosis of Angelman Syndrome

Due to common characteristics that AS shares with other disorders (developmental delays, motor issues, and lack of cooing, babbling or speech), 50% of individuals with Angelman syndrome are originally misdiagnosed. Late or misdiagnosis may cause individuals to lose opportunities for early intervention programs, resources, personalized support or life-changing treatments. Testing and diagnosis of AS is done through a medical doctor.

Diagnosis of Angelman Syndrome

After receiving a diagnosis of Angelman syndrome, many parents are overwhelmed by the fact that they know nothing about the syndrome and the road ahead.

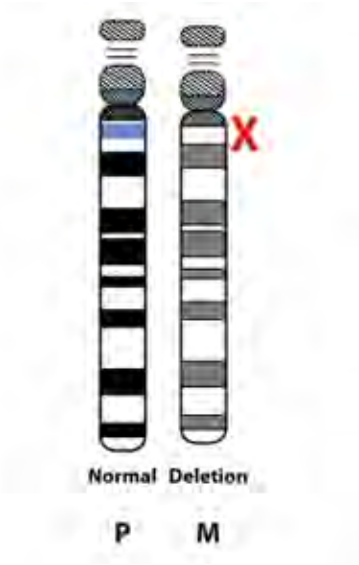
The good news is that we know that an individual with AS is able to do and accomplish more than was believed years ago. Parents were told their child would never walk and never communicate. We know now, that is not true. Early intervention is key. People with AS today are walking, communicating and graduating high school.

Genetics of Angelman Syndrome

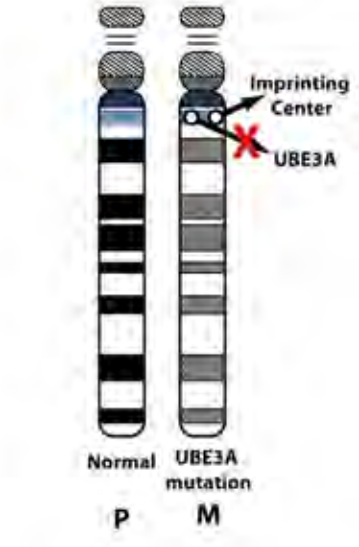
Angelman syndrome is caused by a problem with the UBE3A gene located at the 15th chromosome. It's important to keep in mind that in typical humans, the UBE3A gene from our father is silent and the brain uses the UBE3A gene from our mother during development. There are 4 ways that Angelman syndrome can occur. These are called genotypes. Each genotype has a different mechanism that results in AS.

Genotypes of Angelman Syndrome

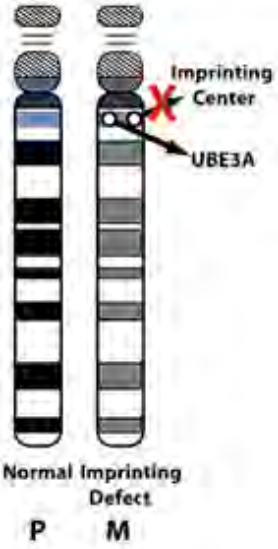
1. Deletion positive
The most common (70% of cases of AS) and occurs when the mother's copy of UBE3A has been deleted and is not present.



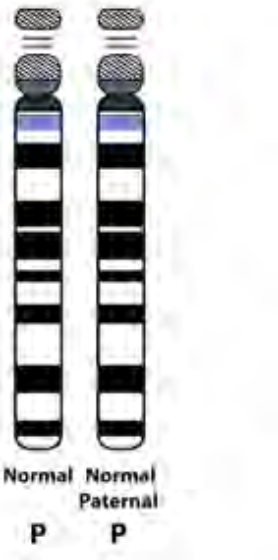
2. Mutation
(11% of cases of AS) occurs when there is a mutation or alteration in the 15th chromosome inherited from the mother. This mutation or alteration either prevents the expression of UBE3A or alters its function.



3. Imprinting Center Defect
6% of cases of AS occurs when there is an abnormality in the imprinting center of the 15th chromosome inherited from the mother. The imprinting center is the area of the chromosome that controls whether genes are turned on or off. So, even though UBE3A from the mother may be present, the problem in the imprinting center makes the UBE3A gene unavailable to the brain.



4. Paternal Uniparental Disomy (UPD)
3% of cases of AS occurs when there are two, number 15 chromosomes from the father, but not one from the mother. Since the UBE3A from the father is silenced or turned off, and the one from the mother is absent, the brain cannot get the information it needs from UBE3A.



Severity of Genotypes in Angelman Syndrome

Unfortunately, the most common AS genotype, deletion positive, tends to be the most severe, in terms of symptoms or characteristics.

Below is an illustration to show the relationship between AS genotypes and the severity of some AS characteristics.

INCREASING SEVERITY

Uniparental Disomy → UBE3A & Imprinting Mutations → Large Deletions

Paternal UPD

- Normocephaly
- No hypopigmentation
- Fewer seizures

Imprinting Defect

UBE3A Mutation

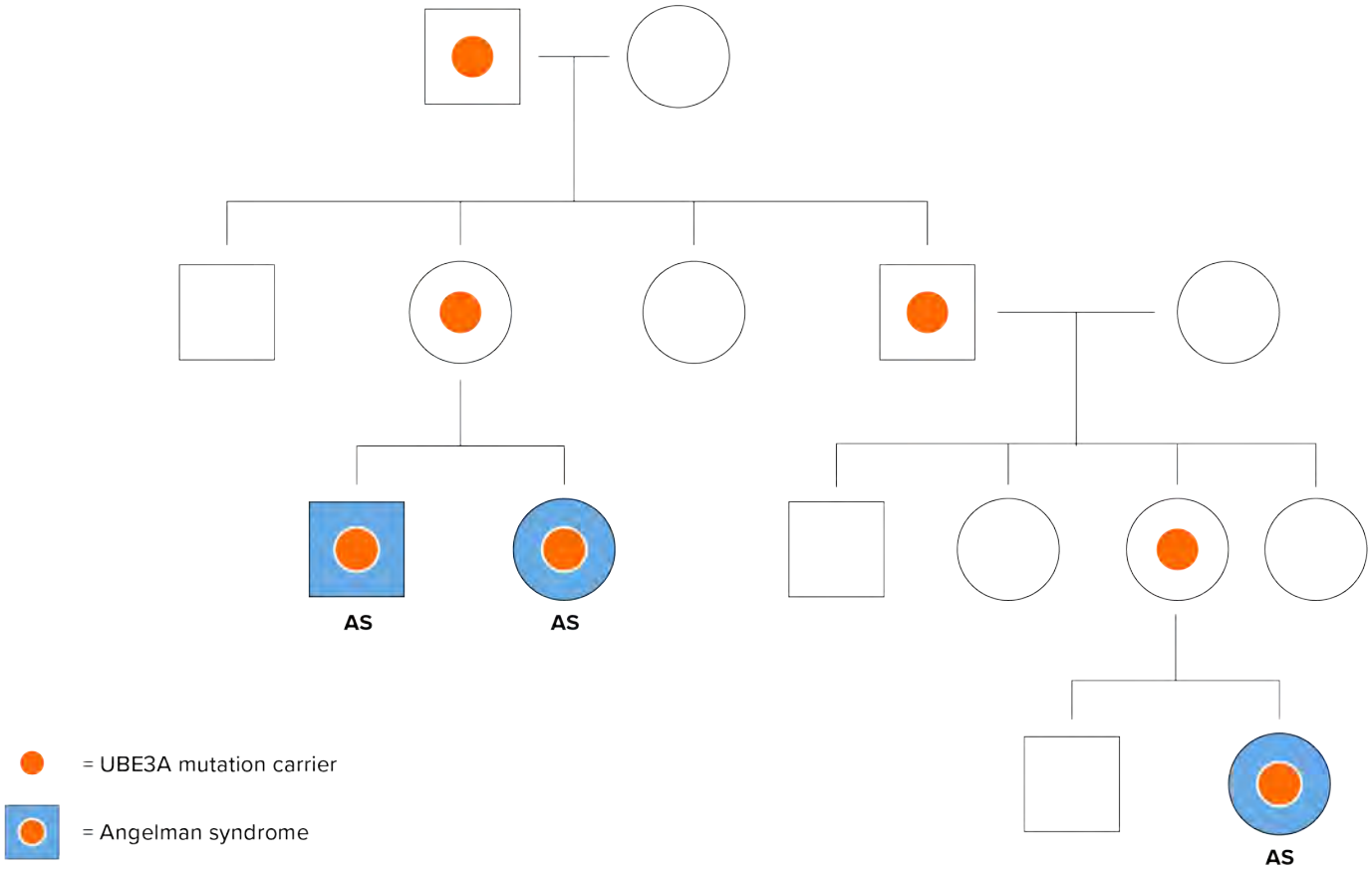
15q11-13 Deletion

- Microcephaly
- Seizures
- Hypopigmentation
- Less weight gain

Risk of Recurrence in Angelman Syndrome

A genetic counselor can inform you on the possibility for Angelman syndrome to occur or recur through gathering family history and blood testing. The following information may be helpful in understanding the genetic risk of Angelman syndrome but is not intended to replace genetic counseling.

EXAMPLE OF IMPRINTING INHERITANCE IN FAMILIAL AS: INHERITED UBE3A MUTATION



1. Common Chromosome Deletion:
More than 98% of the chromosome deletion instances occur by a spontaneous event and thus they are not inherited; the recurrence risk is <<1% for these families. However, 1-2% of deletions occur because of an inherited abnormality in the maternal chromosome 15, such as a balanced chromosome translocation. Another very small group (e.g., only a few cases reported in the literature), can have AS due to a very small, maternally inherited chromosome deletion that involves a small area around and including the UBE3A gene. For these cases, the maternal recurrence risk is increased depending on the type of abnormality present. Chromosome study of the mother, including FISH, helps rule out inherited chromosome 15 abnormalities.

2. Paternal Uniparental Disomy (patUPD):
More than 99% of patUPD cases occur as an apparent spontaneous, non-inherited, event. If an individual has AS due to patUPD and has a normal karyotype, a chromosomal analysis of the mother should nevertheless be offered in order to exclude the rare possibility that a Robertsonian translocation or marker chromosome was a predisposing factor (e.g., via generation of maternal gamete that was nullisomic for chromosome 15, with subsequent post-zygotic "correction" to paternal disomy).

3. Imprinting Center (IC) Defect:
There are two types of IC defects: deletions and non-deletions. Non-deletion events do not appear to be inherited and have a <1% recurrence risk. Most deletions are not inherited but a significant proportion of them are (i.e., maternally inherited), and these confer a 50% risk for recurrence.

4. UBE3A Mutations:
UBE3A mutation can either occur spontaneously (e.g., not inherited and with no increased recurrence risk) or be maternally inherited and have a 50% risk of recurrence (see below for imprinting inheritance).

5. Individuals With No Known Mechanism (All 4 Above Mechanisms Have Been Eliminated):
For parents of AS individuals who have apparent normal genetic tests (no evidence for deletion, imprinting defect, UPD or UBE3A mutation), and thus their children are only clinically diagnosed, it is not known what the recurrence risk is. An increased risk seems likely but probably does not exceed 10%.

6. Germ Cell Mosaicism:
This term refers to a phenomenon in which a genetic defect is present in the cells of the gonad (ovary in the mother's case) but not in other cells of the body. This occurrence can lead to errors in risk assessment because a genetic test, for example on a mother's blood cells, will be normal when in fact a genetic defect is present in the germline cells of her ovary. Fortunately, germ cell mosaicism occurs very infrequently. Nevertheless, it has been observed in AS caused by the mechanisms of large chromosome deletion, Imprinting Center deletion and UBE3A mutation.

7. Imprinting Inheritance:
UBE3A mutations and Imprinting Center deletions can exhibit imprinting inheritance wherein a carrier father can pass on the genetic defect to his children without it causing any problems, but whenever a female passes this same genetic defect on to her children, regardless of the sex of her child, that child will have AS. When an AS genetic mechanism is determined to be inherited, genetic testing of family members can usually identify carriers of the gene defect. As you might imagine, professional genetic counseling is advised in these situations.

For more extensive information regarding Angelman syndrome, its causes, treatment issues and education, we recommend referring to the following resource:

Facts About Angelman Syndrome 7th Edition

Part 2:
Angelman Syndrome Foundation Highlights & Resources

ASF Research Stepping Stones

Since funding its first clinical trial in 1996, ASF-funded research has continued to lay the foundation for future discovery.

UBE3A
ASF funded the first studies of the UBE3A gene. Impairment of this gene causes AS, and these studies helped us better understand how, when and where UBE3A is made. Incremental studies have since followed to understand UBE3A targets, to understand its gene and protein regulation and to understand the structure of the protein.

Mouse Models
ASF funded the first mouse models to help with safe testing of potential therapies and to show how different brain regions contribute to AS symptoms. ASF-funded mouse studies proved that earlier restoration of UBE3A would give better outcomes following genetic therapies.

Gene Therapy
ASF funded the first gene therapy study. This led to funding two more innovative twists to make an optimal gene therapy. These studies, along with the gene activation strategies, have attracted several pharmaceutical companies to develop potential therapies for AS.

ASO Studies
ASF funded the first antisense oligonucleotide (ASO) studies proving that the therapeutic approach would work, which led directly to the three clinical trials by Ionis, Roche and Ultragenyx/Genetx. These studies will help answer questions like: How much ASO and how much UBE3A protein is needed? Is ASO treatment required throughout life? When does ASO treatment need to start?

LADDER Learning Network

For Patients. For Providers. Together, Toward The Cure.
In 2022, ASF and the Dup15q Alliance partnered to launch the LADDER Learning Network to provide high-quality medical care for individuals with AS or Dup15q. The network connects those who practice evidence-based medicine with a high level of excellence for these two rare syndromes. Then, we ensure as many families have access to it as possible through ASF Clinics or Dup15q Clinics worldwide.

Ladder Learning Network Essential Functions

Connects Patients To Care
Connects AS/Dup15q individuals to comprehensive care from highly engaged, highly specialized medical experts who have demonstrated a passion for and an ability to specifically treat these rare disorders.

Connects Providers To One Another
Serves as an avenue for communication among 40+ AS/dup15q experts across the globe to share knowledge, discuss challenging cases and to progress toward standardizing care.

Supports Clinical Trials
Provides a foundation to support clinical trials by having established sites with experts and patients in place to conduct those trials when they become available.

Operates Ladder Database
Operates the global network of patient-powered data, to enhance understanding of both syndromes. Increased insight into data from AS/Dup15q individuals informs better treatment options and will pave the way for a cure.

ASF Clinics Worldwide

ASF Clinics Provide Life-Changing Care Worldwide

With Seizures Controlled, ASF Clinics Helped Our Daughter Grow

"Emily had her first seizure at a year old. Before visiting the ASF Clinic at Children's Hospital Colorado, she was having multiple seizures in a 24-hour period once a month. At the clinic, she saw a team of doctors, therapists and other specialists who focus on caring for kids with AS. They gave Emily a new seizure medication and developed a care plan to reduce her seizures and aid her development. She hasn't had a seizure since November 2021. It is a dream come true!"

— The Waibel Family

"ASF Clinics are the ultimate resource for the AS community. Families can access expert care, access clinical trials and access future treatments for those living with AS. Clinics are one of the key resources needed for this community, and we are so thankful that ASF answered that call."

Ron Thibert, DO, MSPH — ASF Clinician at Massachusetts General Hospital

ASF Clinic	Location	Specialties
Boston Children's Hospital	Boston, MA	Genetics, Neurology, Developmental Pediatrics, Psychology, Sleep, Gastroenterology, Orthopedics **LADDER Database Site, Clinical Trial Site*
Boys Town National Research Hospital	Boys Town, NE	Genetics, Neurology, Sleep, Psychology, Gastroenterology and Nutrition
Children's Hospital Colorado	Aurora, CO	Genetics, Neurology, Developmental Pediatrics, Diet and nutrition, Rehabilitation Medicine, Occupational Therapy, Physical Therapy, Social Work, Speech Therapy *AS Center of Excellence, LADDER Database Site
Children's Hospital of Eastern Ontario	Ottawa, Ontario	Neurology, Developmental Pediatrics, Genetics, Psychology
Children's Hospital Los Angeles	Los Angeles, CA	Neurology, Genetics, Psychology, Speech Therapy, Social Work *Dup15q Center of Excellence, LADDER Database Site
Children's Mercy Kansas City	Kansas City, MO	Neurology, Psychiatry, Psychology, GI, Genetics, Orthopedics, Ophthalmology, Speech, Nutrition, Physical Therapy, Occupational Therapy and Social Work
Geisinger Autism & Developmental Medicine Institute	Lewisburg, PA	Developmental Assessments, Psychological and Educational Testing, Genetic Counseling, Medication Management, Neurology, Behavior
Kennedy Krieger Institute	Baltimore, MD	Neurology & Neurodevelopment Medicine, Genetics, Speech Language Pathology, Physical/Occupational Therapy, Social Work
Massachusetts General Hospital	Boston, MA	Neurology, Epilepsy, Psychiatry, Neuro-Psychology, Gastroenterology, Sleep *AS Center of Excellence, Dup15q Center of Excellence, LADDER Database Site
Mayo Clinic	Rochester, MN	Clinical Genomics, Epilepsy, Sleep, Speech therapy, Behavioral, Physical Medicine
Minnesota Epilepsy Group	St. Paul, MN	Neurology, Neuropsychological Testing, Psychiatry
Nicklaus Children's Hospital	Miami, FL	Neurology, Genetics, Nutrition, Psychology, Social Work
NYU Langone Health	New York, NY	Epilepsy, Psychiatry, Neuropsychology, Nutrition, Gastroenterology, Speech Pathology/Rehabilitation Services

ASF Clinic	Location	Specialties
Rady Children's Hospital San Diego	San Diego, CA	**Clinical Trial Site*
Rush University Medical Center	Chicago, IL	Neurology, Developmental-Behavioral Medicine, Sleep Medicine, Gastroenterology, Genetic Counseling, Psychology, Psychiatry, Speech Language Pathology, Rehabilitation Medicine, Physical Therapy, Occupational Therapy, Pulmonology **AS Center of Excellence, LADDER Database Site, Clinical Trial Site*
Texas Children's Hospital	Houston, TX	Genetics, Neurology, Physical Medicine & Rehabilitation, Developmental Pediatrics **Clinical Trial Site*
UCSF Benioff Children's Hospital	San Francisco, CA	Epilepsy, Movement Disorders, Development and Behavior Issues, Sleep Disorders **LADDER Database Site*
UNC Carolina Institute for Developmental Disabilities	Carrboro, NC	Genetics, Neurology, Psychiatry, Psychology, Speech and Language Pathology, Occupational and Physical Therapy, Social Work **AS Center of Excellence, Dup15q Center of Excellence, LADDER Database Site, Clinical Trial Site*
Vanderbilt University Medical Center	Nashville, TN	Pediatric Neurology, Sleep Neurology, Nutrition, SLP Services - AAC Device Focus **LADDER Database Site*
Weill Cornell Medicine	New York, NY	Pediatric Medicine, Neurology, Genetics, Psychiatry, Psychology, Speech Language Pathology, Physical/Occupational Therapy, Social Work, Nutrition

Europe & Asia — ASF Clinic Locations

ASF Clinic	Location	Specialties
Erasmus MC Sophia Children's Hospital	Rotterdam, Netherlands	Neurology, Psychology, Speech and Language/AAC, Physical Therapy, Diet and Nutrition, Behavior and Development Management
Angelman Center Munich	Munich, Germany	Speech and Language, Physical Therapy, Behavior, Nutrition and Diet (including Ketogenic Diet), Orthopedics and Gait Analysis
Angelman Center Aachen	Aachen, Germany	Speech and Language, Physical Therapy, Behavior, Nutrition and Diet, Orthopedics

Middle East — ASF Clinic Locations

ASF Clinic	Location	Specialties
Edmond and Lily Safra Children's Hospital	Sderot Gabriela, Ramat Gan, Israel	Neurology, Psychiatry, Endocrinology, Dietician, Orthopedic Surgery

South America — ASF Clinic Locations

ASF Clinic	Location	Specialties
Buenos Aires, Argentina	Buenos Aires, Argentina	Neurology, Orthopedics, AAC and Assistive Technology, Development and Learning, Occupational Therapy, Sensory Integration

Angelman Syndrome Helpful Information

About Angelman Syndrome Fact Sheet

Angelman Syndrome Foundation PSA Video

Angelman Syndrome Journey Brochure

ASF Podcasts

What does ASF Mean To You Video

Clinical Trial Patient Retention Education Video

Conducting clinical trials in Angelman syndrome research is key to improving the lives of individuals with Angelman syndrome and to finding a cure.
In recent years, there have been critical discoveries that have greatly improved our understanding of Angelman syndrome and have led to critical discoveries, clinical trials and increased funding by the NIH.

View the Clinical Trial Patient Retention Education Video

Part 3:
Conducting Clinical Trials In AS

As sites prepare to run clinical trials in AS, it is essential that research teams understand the key elements of site readiness, including but not limited to: training (research, protocol, and specialty specific), regulatory/institutional (IRB) requirements, and the tools (such as SOPs, forms, templates, etc.) that are needed to support the team in the effective conduct of a trial, across a study life cycle. This also necessitates a healthy understanding of the patient community, with a rare disease. This next part of the resource addresses key attributes of site readiness and the types of things that sites will need to think about as they prepare for and conduct clinical trials. Throughout, attention is given to specific considerations and challenges that may arise in the context of AS clinical trials specifically, due to the nature of the disease and the needs of AS patients.

Before You Begin: Adopting a Collaborative, Patient-Focused Approach

Before delving into the specifics of site preparedness or the logistics of running a clinical trial, it can be helpful to think about the mindset with which you approach clinical trials, and how you can adopt a patient-focused mindset. Increasingly, collaborative, patient-focused approaches are being emphasized in health care and drug development. Taking a patient-focused approach has been shown to increase the success of clinical trials and can be applied to all aspects of clinical trial operations. This type of approach emphasizes the needs of the patient, involves assessing trial design and operations from a patient perspective and may in certain cases even include integrating AS patient community input directly into the clinical trial design. In general, understanding patient perspectives may help sites involved in conducting trials to be more effective, and streamline the patient experience during trials.

In an AS clinical trial, a patient-focused approach can be particularly impactful. AS clinical trials may have more intensive protocols and procedures and can require significant commitments on behalf of the patients, their families, and their caregivers. This commitment is on top of the daily challenge that these patients and families have in managing care and coping with the implications of the patients' diagnosis with a genetic neurological disease. During the trial, patients and families may need reassurance; they may need someone who can listen to their questions, concerns and struggles. Furthermore, the families, caregivers, and the patients themselves tend to be very involved in care and want to be involved in the trial process.

In planning for and conducting clinical trials, trial sites can help to create a positive experience for patients by, as appropriate and feasible, taking a proactive approach to streamlining care and promoting a patient-focused mindset among key team members involved in trial conduct. This starts with trial planning and recruitment and carries through until the trial concludes.

Site Preparedness for Clinical Trials in AS

Although each clinical trial is unique and the needs of sponsors will vary from one trial to the next, there are a number of factors that are likely to impact a site's preparedness for trials regardless of individual study needs. These include the site's infrastructure and ability to support clinical trials as well as the experience and abilities of key members of the research team and site staff.

Before getting into the specifics of planning for and running a clinical trial in AS, it may be helpful to review these factors to determine whether there are any steps that your site may need to take to become trial-ready.

The AS Clinical Trial Program is a voluntary, educational program designed to help sites - especially new AS trial sites - assess their preparedness and identify opportunities to increase their site and staff's readiness to run AS clinical trials. This evaluation is part of ongoing efforts by the Angelman Syndrome Foundation to increase trial site capacity and optimize readiness throughout the United States, to better meet the needs of trial sponsors and the AS patient community as the number of AS clinical trials increases. Participation in the preparedness program helps sites to:

a. Access resources that equips clinical research staff to conduct AS trials,
b. Acquire visibility with sponsors who may be seeking new trial sites.

If you are interested in learning more about this preparedness evaluation process, please contact the Angelman Syndrome Foundation.

The Research Team: Key Players in AS Trials

Principal Investigators
Principal Investigators (PIs) are tasked with the responsibility of providing the primary level of oversight of clinical trial conduct by ensuring that all associated research staff comply the protocol as well as all IRB and FDA rules and regulations. PIs are also required to provide oversight of record management including documentation of informed consent, randomization, and protocol deviations. The use and distribution of investigational drug is also monitored by the PI. Should adverse events occur, the PI must also assess the status of the subject and provide notification to the sponsor as well as the IRB and FDA when applicable. Please note, although sites are encouraged to delegate study related procedures, the PI must ensure that staff is appropriately credentialed and trained to complete the assigned task (Baer, Devine, Beardmore, & Catalano, 2011; National Drug Abuse Treatment Clinical Trials Network, n.d.; International Council for the Harmonisation for International Requirements of Technical for Pharmaceuticals for Human Use (ICH)., 2016).

For a detailed description of the role and responsibility of principal investigators please see section 4 of the Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2), and Baer, Devine, Beardmore, and Catalano, Clinical Investigator Responsibilities (2011).

Clinical Research Coordinators
Clinical Research Coordinators (CRCs), also known as Study Coordinators (SCs), work with principal investigators (PIs) to conduct clinical trials using good clinical practices (GCP). CRCs are the main communication liaison between the investigators and the study subjects, as well as the site and the sponsor. CRCs also handle a great deal of the everyday study activities. While every CRC's responsibilities may differ, key activities may also often include Institutional Review Board (IRB) submissions, negotiating contracts and budgets, and ensuring integrity and ethics

in the study and site's conduct. The CRC role continues to increase in both amount of responsibility given, and tasks assigned, as well as overall importance. A high-performing clinical research coordinator (CRC) is critical to the success of any clinical trial, but this is especially true in AS clinical trials given the complex needs of this patient community.

Because this position has such varied responsibilities and serves such a critical function in clinical trials, it is imperative that CRCs are properly trained and have access to a wide range of tools and resources. When supporting AS clinical trials, CRCs may also encounter a number of specific disease-related challenges as well as challenges related to conducting clinical trials in rare diseases, and coordinators can benefit from the knowledge sharing of experienced AS trial staff.

Key Elements of Trial Management

As sites and their research teams prepare for clinical trials in AS, it will be helpful to ensure that research teams have a firm grasp on familiar elements of trial management - such as good clinical practice, standard operating procedures, recruitment and retention - and are sensitized to potential challenges that may arise in AS clinical trials as a result of the complexity of the disease and patient needs. This next section provides an overview and information about suggested resources on good clinical practice, the ethical conduct of trials, standard operating procedures, documentation, monitoring and quality assurance, as well as key activities and issues related to patient recruitment and retention.

Good Clinical Practice

The principles of Good Clinical Practice (GCP) help to assure the safety, integrity, and quality of clinical trials by addressing elements related to the design, conduct, and reporting of clinical trials. Per the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice:

> *"Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible."*

ICH E6(R2) provides extensive detail on GCP, including the roles and responsibilities of key parties including the institutional review board, investigators, and sponsors as well as information on the clinical trial protocol and investigator's brochure.

All research staff are required to complete and maintain certification in Good Clinical Practice. GCP training describes the responsibilities of investigators, sponsors, monitors, and IRBs in the conduct of clinical trials. A listing of free training resources can be found in Appendix C of this document.

Ethical Conduct of Research: An Essential Element of Good Clinical Practice
Ethical considerations must be integrated into all aspects of clinical trials, from the training of health care professionals and staff prior to trial conduct, through the planning, conduct and completion of trials. These are a key part of Good Clinical Practice and important for protecting the welfare of research subjects. Key principles related to the ethical conduct of research include the social and clinical value, scientific validity, fair subject selection, favorable risk-benefit ratio, independent review, informed consent, and respect for potential and enrolled subjects.

To ensure that the individuals involved in planning and conducting trials understand and can identify key ethical issues that may arise in human subjects' research, all staff members and health care professionals involved in human subject's research will be required to complete ethics training. In addition, an Institutional Review Board (IRB) must oversee and review the ethics of every clinical trial. Their goal is to protect human subject welfare. IRBs must be involved in the clinical trial process from the start, by reviewing all protocols and materials prior to the study.

Standard Operating Procedures
Standard operating procedures (SOPs) are policies that include a detailed set of instructions designed to regulate outcomes of routine activities. Frequently, SOPs are implemented to maintain uniform consistency while adhering to regulations, and institutional policies, in addition to providing greater clarity about workflow.

Development and implementation of standard operating procedures for all major aspects of clinical trial activities is strongly encouraged. Although sites will need to develop SOPs based upon their specific attributes and trial needs, SOPs should address, at a minimum:

- Trial participation recruitment and retention
- The informed consent process
- Document management, including filing and recordkeeping
- Institutional review board review
- Protocol deviation and violation documentation, resolution, and reporting
- Adverse event documentation, resolution, and reporting
- Study closure

For reference, links to sample SOPs are included in the Appendix B.1 table located in this document.

Documentation
Trial sponsors and investigators participating in clinical trials must prepare and maintain a wide variety of documents during the lifecycle of a clinical trial. These documents play an important role in demonstrating that the investigator, sponsor and monitor are complying with the standards of Good Clinical Practice and all applicable regulatory requirements; they can also assist with successful trial management and confirming the validity of trial conduct and assuring data integrity.

Essential Documents Needed Before, During, and After Clinical Investigations
Section 8 of the Integrated Addendum to ICH E6 (R2): Guideline for Good Clinical Practice provides in-depth information on essential documents that should be prepared before, during, and after the conduct of a clinical trial. While it is important that investigators adhere to sponsor, IRB, and/or applicable regulatory body requests, this guideline provides baseline understanding of essential documents.

Monitoring and Quality Assurance
Trial monitoring and quality assurance take place throughout the clinical trial and are an important part of ensuring that human subjects' rights are protected; trial data are accurate, complete, and verifiable; and that trial conduct complies with the protocol, GCP, and regulatory requirements. The study sponsor will be responsible for selecting qualified study monitors and ensuring adequate monitoring of the study; however, sites should also develop reliable quality control processes and an audit plan.

If deviations from the protocol, GCP, or regulatory requirements are identified, prompt action will be needed to address them. Corrective actions may involve staff training or creation of new SOPs, tools and templates. All potential corrective actions should be tested prior to implementation to verify that they address the problem and can be incorporated within current procedures relatively easily.

Patient Recruitment, Screening, Consent, and Retention

Recruitment
Patient recruitment is one of the most important - yet also time-consuming and potentially costly - aspects of the clinical trial process. Under the guidance of the investigator, research staff are tasked with the responsibility of increasing awareness of clinical trial opportunities and identifying individuals eligible for enrollment in clinical trials. Without an effective patient recruitment strategy, sites may fail to connect with potentially eligible patients, miss deadlines due to low enrollment, or miss the opportunity of enrolling patients, all together, if site is involved in a competitive enrollment process (Tweet, 2011).

Challenges in Recruiting Patients for AS Trials
Timely and efficient recruitment is vital to ensure an optimal trial outcome in a rare disease such as AS, and the rarity of AS means patients are often geographically dispersed. As such, it may be more difficult to connect with and recruit patients for trials. It also means that many patients will need to travel a significant distance to reach a center conducting trials in AS.

Strategies to Address Recruitment Challenges
To address these challenges, trial sites may find it helpful to have a communication plan and to incorporate innovative recruitment strategies into these plans. One way for sites and their staff to connect with a larger segment of the geographically disperse patient community and to increase opportunities for recruitment is by working with patient advocacy groups, local groups that provide support and services, and by engaging with the patient community (ACRP, n.d; AccrualNet, 2013).

Patient advocacy groups, such as ASF, also maintain AS patient contact registries to connect interested individuals with particular trials. Establishing good relationships with referring sites can also aid in recruitment. Alternative advertising platforms, communication strategies, and consideration of patient barriers (e.g., travel challenges) can also help support efficient recruitment (Augustine, Adams, & Mink, 2014; International Rare Diseases Research Consortium (IRDiRC), 2016; Tweet, 2011). For example, social media can provide a direct and cost-efficient advertising platform to target populations for clinical research, thus increasing awareness of clinical trials and helping to inform potential participants of eligibility requirements-particularly for patients who are not located near Centers of Excellence (Krischer et al., 2017; Shpilber, 2017). However, there is a continuing discussion on the benefits of utilizing social media to engage prospective participants and on the ethical considerations that should be addressed when utilizing social media (Krischer et al., 2017; Gelinas et al., 2017).

Sites should be aware that social media is a powerful communication tool that parents and caregivers may turn to for input on clinical trials (Murphy, 2016). However, the information that is shared by other patients on social media can lead to unrealistic expectations about interventions. Research teams may wish to be prepared to address these potential misconceptions and to caution participants, parents, and caregivers about relying on unofficial results or feedback from other participants on social media (CURE SMA: Clinical Trial Readiness Toolkit, 2021).

Screening
Before a research participant can enter a clinical trial, he/she must undergo a screening process. The screening process allows the study investigator/sponsor/team to determine if an individual is eligible to participate in a study. An IRB approved study protocol, including the study procedures to conduct during a screening visit, is used to ascertain the eligibility of potential research participants into a clinical trial.

Informed Consent
At the outset of any interaction with an individual for research purposes, all staff must initiate the informed consent. Obtaining valid and appropriate informed consent is a crucial part of protecting human subjects' rights and welfare: every member of the research team must recognize this and ensure that proper consent is obtained for all research subjects before any trial-related procedures are conducted.

Research teams are encouraged to view informed consent as a process that continues throughout the trial, and to regularly revisit aspects of informed consent relevant to activities being carried out as part of the trial. For successful implementation, in addition to the provision of the consent document, it is crucial for staff to discuss the purpose of the protocol along with any benefits and risks to participation. Staff must also provide ample time for the individual to consider the information provided and discuss concerns with friends, family, and research staff especially the investigator. The FDA offers a comprehensive review of the informed consent process as follows:

> *"To many, the term informed consent is mistakenly viewed as the same as getting a research participant's signature on the consent form. FDA believes that obtaining a research participant's verbal or written informed consent is only part of the process. Informed consent involves providing a potential participant with:*

- Adequate information to allow for an informed decision about participation in the clinical investigation.
- Facilitating the potential participant's understanding of the information.
- An appropriate amount of time to ask questions and to discuss with family and friends the research protocol and whether you should participate.
- Obtaining the potential participant's voluntary agreement to participate.
- Continuing to provide information as the clinical investigation progresses or as the subject or situation requires." (U.S. Food & Drug Administration, 2018)

For additional information linked to implementation of the informed consent process, please review additional FAQ's listed on the FDA website. National Institute of Health's Good Clinical Practice Training (NIH, 2017).

Considerations for the Informed Consent Process in AS
For many AS clinical trials, it is likely that parents of the AS patients will provide the consent in order for the patients to participate in the clinical trial. Past clinical trials of rare diseases have found that due to the increased pressure and burden that the parents are dealing with, informed consent becomes a challenge. Understanding the challenges and ethical issues associated with the informed consent process for AS patients - and understanding strategies for addressing these challenges - may help sites to more effectively navigate the informed consent process.

The following proposed strategies were developed to help research teams navigate the informed consent process:

- In terms of general approach, research teams may find it helpful to think about the informed consent process as a continuing dialogue with parents and patients throughout the clinical trial experience (Steinhillber, 2015; Joseph, Craig, & Caldwell, 2015).
- When obtaining consent, having a physician present - or having the physician obtain consent from the parents themselves - may help parents develop trust, which is essential to increasing the chances of consenting (Steinhillber, 2015). Other practical considerations such as printing multiple copies of the informed consent form, one for the CRC and one for each caregiver, so that parents can follow along as the CRC reviews the form can also be helpful.
- Flexibility is another factor to keep in mind when obtaining consent. Clear and consistent communication is important, and it may be possible for research staff to adjust how they communicate key points based on each family and their circumstances (Steinhillber, 2015; Joseph, Craig, & Caldwell, 2015).

Safety and Adverse Events
ICH E6(R2) defines adverse drug reactions, adverse events, and serious adverse events as follows:

<u>1.1 Adverse Drug Reaction (ADR)</u>
In the preapproval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship

between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Regarding marketed medicinal products: A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

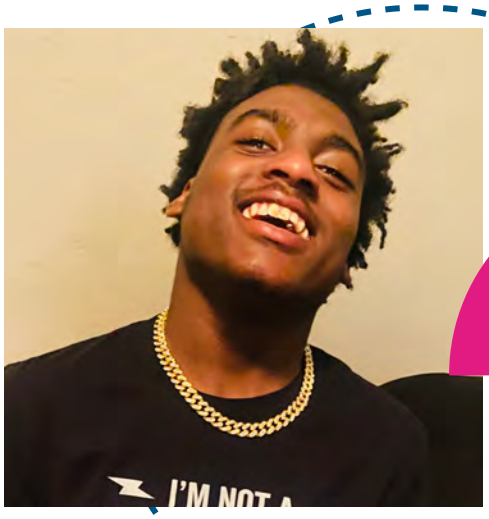
1.2 Adverse Event (AE)
Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.3 Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)
Any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Adverse events are taken seriously in clinical trials and must be documented and addressed in accordance with the trial protocol, GCP, and any applicable regulatory guidelines.

For additional resources regarding reporting adverse events to IRBs, please see the FDA's Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs - Improving Human Subject Protection (FDA, 2009).



Part 4:
Patient Experience & Practical Considerations

Practical Angelman Syndrome Guidance for Site and Hospital Staff

What Every Staff Member Should Know
Not every person interacting with an Angelman family will be a principal investigator or study coordinator. Front desk staff, anesthesia teams, PACU nurses, transporters, phlebotomists, EEG techs, security staff, inpatient nurses, and rotating personnel may all influence the safety and experience of a trial day.

For many families, the quality of these interactions matters just as much as protocol execution.

This section is intended as a practical reference for any staff member who may encounter an individual with Angelman syndrome during a trial visit.

Common Behaviors and Presentations Staff May See

- Individuals with Angelman syndrome may:
- Smile or laugh frequently, even when anxious, overstimulated, or uncomfortable
- Have limited or no verbal speech
- Communicate through vocalizations, gestures, AAC, facial expressions, or behavior
- Show excitement through movement, grabbing, reaching, flapping, vocalizing, or sudden activity
- Have short attention spans or difficulty tolerating waiting
- Seek movement or resist stillness
- Be highly sensory-sensitive to lights, sounds, transitions, touch, or unfamiliar environments
- Have difficulty expressing pain, fear, nausea, dizziness, or discomfort clearly
- Escalate quickly when routines change or when they do not understand what is happening

Staff should not assume that smiling means comfort, that quiet means calm, or that distress will always look obvious.

What Families Want Staff to Know
Families are usually the best source of practical guidance for that individual child or adult. Parents and caregivers often know:

- What anxiety looks like for their loved one
- How pain is expressed
- What sensory triggers may escalate distress
- What calms, comforts, or redirects effectively
- Whether touch, separation, noise, bright lights, or waiting are likely to be difficult

When in doubt, ask the caregiver first.

Practical Tips for Staff
Small adjustments can make a major difference.

Helpful Approaches

- Smile warmly and greet both the caregiver and participant respectfully
- Use simple language, short phrases, and visual or gestural cues
- Give one direction at a time
- Allow extra processing time
- Follow the caregiver's lead on interaction style when appropriate
- Offer movement breaks or space to walk, when safe
- Provide estimated wait times and keep families updated
- Reduce unnecessary transitions when possible
- Prepare rooms, supplies, and staff before bringing the family in
- Consider texting or calling families when the room is ready, if it is safer and easier than prolonged waiting room time
- Ask what works before problems arise

Things to Avoid

- Long, unexplained waits
- Bright, noisy, crowded, or overstimulating spaces when avoidable
- Separating the participant from the caregiver without preparation
- Assuming nonverbal means unaware
- Speaking only to the caregiver and not acknowledging the participant
- Leaving tempting objects within reach, such as phones, badges, lanyards, stethoscopes, or dangling items
- Wearing long loose hair or unsecured accessories if grabbing is likely
- Expecting the participant to remain idle for long periods in prep, PACU, or waiting areas
- Changing plans abruptly without explanation

Questions Staff Should Feel Comfortable Asking Parents

To prepare appropriately, site staff should feel empowered to ask caregivers practical questions such as:

- What does anxiety look like for your child?
- How does your child show pain or discomfort?
- What usually helps calm them?
- Are there common triggers we should avoid?
- Is touch helpful or upsetting?
- How do they usually respond to waiting?
- What communication methods work best?
- Are there words, routines, songs, or objects that help?
- Is separation from you likely to be distressing?
- What should we know before we begin?

These questions signal respect, improve planning, and reduce preventable distress.

Trial Implications for Ancillary Staff

For ancillary staff such as PACU nurses, anesthesia teams, transport staff, front desk personnel, and rotating hospital teams, Angelman syndrome may present differently than other neurologic or neuromuscular conditions they have encountered.

For example, a site may have prior ASO experience in SMA and feel highly comfortable with lumbar puncture workflows or inpatient monitoring. However, the lived experience of Angelman syndrome can differ substantially in ways that affect the day:

- Communication barriers may make pain or side effects harder to detect
- Sensory sensitivities may heighten distress in routine hospital environments
- Behavioral responses may be misread if staff are unfamiliar with Angelman syndrome
- Waiting, transitions, recovery, and separation may be more disruptive than anticipated
- Parents may need to remain central throughout the visit to support regulation and communication

What this means for site teams:

- Operational readiness alone is not enough. Site preparedness should include basic Angelman-specific education for all staff who may interact with the family that day.
- Where possible, sites should consider a brief in-service or reference sheet for staff that reviews:
- Common Angelman behaviors and communication differences
- Sensory and anxiety considerations
- Parent-guided calming strategies
- Safety considerations in waiting, pre-op, procedure, and recovery settings
- The importance of avoiding assumptions based on smiling, age, or nonverbal status

Resources for Families Participating in Clinical Trials

Role of the Angelman Syndrome Foundation (ASF)

ASF serves as a trusted bridge between families and the research ecosystem. Many families turn to ASF first, not sponsors, when they are deciding whether to participate or when challenges arise mid-trial.

Clinical Trial Education and Navigation

ASF provides families with:

- Plain-language explanations of trial phases and goals
- Clear descriptions of placebo, randomization, and blinding
- Realistic expectations around timelines and uncertainty
- Support in preparing questions for investigators

Why this matters:

Families who understand the why behind a protocol are more confident, less anxious, and better retained.

Clinic and Care Coordination

ASF supports:

- Coordination with specialty clinics familiar with Angelman syndrome
- Guidance for local providers supporting trial-related care
- Education to prevent conflicting medical decisions

Why this matters:
Trials rarely replace routine care, coordination prevents gaps and risk.

Family Support Resources
ASF helps families manage:

- Travel logistics
- Scheduling strain
- Educational disruption
- Caregiver overwhelm
- Mental Health Support

Best practice:
Investigators should proactively share ASF resources at screening, not only when challenges arise.

Standards of Care in Angelman Syndrome
Angelman syndrome standards of care are built on decades of collective clinical and family experience. Many families have spent years stabilizing medication regimens, sleep routines, therapies, and communication supports.

Why This Matters for Trials
Protocols that disrupt standard care, even unintentionally, can:

- Trigger seizure instability
- Worsen sleep deprivation
- Cause regression in skills
- Increase family distress

Investigator Responsibilities

- Design protocols that respect medication stability
- Avoid unnecessary therapy interruptions
- Coordinate with existing providers
- Clearly explain why deviations are required

Ignoring standards of care does not just increase burden, it risks safety and data integrity.

Mental Health and Psychosocial Support for Trial Families
Clinical trial participation in Angelman syndrome is emotionally layered and psychologically demanding. For many families, enrolling in a trial is not simply a research decision, it is a deeply personal act shaped by years of caregiving, advocacy, and lived experience with uncertainty.

A Dynamic Emotional Landscape
Families often experience multiple, sometimes conflicting emotions throughout the trial lifecycle, including:

- Hope tied to the possibility of improvement or stabilization
- Fear of adverse effects, regression, or unforeseen complications
- Guilt related to decision-making on behalf of a nonverbal loved one
- Grief when expectations are not met or when outcomes fall short

These emotions are not static. They often intensify at key moments, screening, first dosing, adverse events, protocol changes, unblinding, or trial close-out, and may fluctuate even during periods of clinical stability.

The Weight of Decision-Making
Caregivers often carry the emotional burden of making irreversible decisions for someone who cannot consent for themselves.

Accumulated Grief and Loss
For families who have participated in multiple studies, each trial outcome, especially those that fail or end early—can add to a growing sense of cumulative grief.

Ethical Trial Practice Requires Psychosocial Awareness
Supporting mental health is not separate from scientific rigor, it is integral to ethical research conduct.
Ethical trial practice includes:

- Normalizing emotional responses and explicitly acknowledging that mixed feelings are expected
- Checking in with families beyond clinical endpoints, particularly after stressful events or major milestones
- Recognizing sibling impact, including anxiety, disrupted routines, and emotional strain
- Referring families proactively to ASF mental health and psychosocial support resources rather than waiting for crisis points

Why This Matters for Trial Outcomes
Unaddressed psychosocial strain can:

- Contribute to missed visits or protocol deviations
- Increase withdrawal rates unrelated to safety or efficacy
- Undermine trust between families and study teams
- Shape community perception of research programs

Conversely, families who feel emotionally supported are more likely to:

- Remain engaged through trial completion
- Communicate concerns early and clearly
- Participate in follow-up studies
- Serve as informed advocates for ethical research

ASF Mental Health Support Access
The Angelman Syndrome Foundation offers free mental health counseling to individuals with Angelman syndrome, caregivers, and siblings across the community.
Trial teams are encouraged to:

- Inform families of this resource early in the trial process
- Normalize use of mental health support as part of comprehensive care
- Refer families proactively, not only in moments of crisis

Burden Awareness and Protocol Flexibility
Trial participation often requires families to absorb:

- Long-distance travel
- Missed work and lost income
- School disruption
- Sibling caregiving logistics
- Sleep loss and physical exhaustion

Thoughtful design includes:

- Flexible visit windows
- Remote or hybrid assessments when possible
- Minimizing duplicative procedures
- Recognizing cumulative burden over time

Reducing burden improves both ethics and data quality.

Communication Expectations
Families value honesty over optimism.
Effective communication means:

- Clear timelines, even when uncertain
- Prompt updates when plans change
- Avoiding exaggerated promises
- Transparent discussion of risks and unknowns

Silence or delayed communication erodes trust faster than bad news.

Historical Context and Community Memory
Some families enter trials with:

- Extensive trial experience
- Strong scientific literacy
- Past trauma or disappointment

Others are new and overwhelmed.

Best practice:
Ask about prior trial experience
Acknowledge what families bring with them
Create space for concerns rooted in history
This awareness creates safer, more respectful engagement.

Post-Trial Considerations and Follow-Through
The conclusion of a clinical trial is not merely a procedural milestone, it is often an emotionally significant moment for families who have invested time, energy, hope, and trust in the research process.

Families frequently leave a trial asking:

- What happens now?
- What did our participation actually contribute to?
- Did this help our child, or help others?

Ethical Follow-Through Extends Beyond Data Collection
This includes:

- Sharing results in accessible, plain-language formats
- Providing realistic timelines for data analysis, publication, and regulatory steps
- Communicating clearly when results are inconclusive or negative
- Clarifying post-trial access options, compassionate use pathways, or follow-on studies when applicable

Acknowledging Emotional Impact
Trial teams should recognize that families may experience grief, frustration, anxiety, or loss at close-out.

Closing the Loop as an Act of Partnership
Families who feel respected and informed at trial close-out are more likely to engage in future research and remain trusted partners in the field.

Angelman Syndrome Patient-Focused Drug Development (PFDD)
ASF's PFDD process centered lived experience across the lifespan and identified:

- Symptoms that matter most to families
- Outcomes beyond traditional endpoints
- Risk tolerance shaped by real caregiving realities

PFDD findings offer a roadmap for ethical, family-centered trial design grounded in real life, not theory.

Resources You Can Share With Families to Prepare for the Trial

Pre-Visit Checklist for Families: Preparing for Interventional Clinical Trials
Participating in a clinical trial is a big step, and we want to help make your experience as smooth and informed as possible. Please review and complete this checklist before your visit.

1. Understand the Trial Basics

- Review the informed consent form and bring any questions with you
- Know the trial phase, purpose, and what the investigational treatment is intended to do
- Confirm whether this is a blinded or open-label trial
- Understand randomization, if applicable, and what group your child may be assigned to

2. Gather Documentation

- Bring a copy of your child's most recent medical records, including:
  - Neurology notes
  - Seizure logs
  - Therapy reports such as PT, OT, and speech
  - Genetic testing results
  - Growth charts and immunization records
- Print and bring a list of current medications and supplements, including doses and times
- Create a seizure diary or behavior log from the last 2–4 weeks, if required by the protocol

3. Prepare for Assessments

- Be aware of any baseline evaluations your child will undergo, such as bloodwork, EEG, MRI, or behavioral assessments
- Talk to your care team about how to prepare your child for these assessments, including sedation or fasting
- Bring comfort items, snacks, and sensory supports for long wait times

4. Coordinate With the Trial Site

- Confirm your appointment date and time and expected duration of the visit
- Ask about pre-visit fasting, medication restrictions, or special instructions
- Verify clinic location, parking information, and where to check in
- Request contact info for a study coordinator or nurse in case you need support day-of

5. Plan for Travel and Accommodations

- Book hotel accommodations if overnight stay is needed and ask if the site offers discounts
- Bring a travel folder with:
  - ID cards
  - Insurance cards
  - Site contact info
  - Trial paperwork
- Pack essentials such as comfort items, extra clothes, headphones, snacks, medications, and sensory supports

6. Communication and Consent

- Review and bring all legal guardianship or custody paperwork, if applicable
- Prepare a list of questions to ask the principal investigator or study team
- Ask about how data will be shared, potential risks and benefits, and post-trial access to treatment

7. Reimbursement and Support

- Ask about travel reimbursement, per diem, or coverage for meals and hotels
- Inquire about compensation for participation, if applicable
- Confirm whether you need to save receipts for reimbursement

8. Emotional Preparation

- Talk as a family about what to expect and identify fears or concerns
- Bring a friend or co-caregiver for support if possible
- Schedule some time for fun or relaxation before or after the visit if travel is involved

If you have questions before your visit, do not hesitate to contact your study coordinator. You are not in this alone—we are here to support you every step of the way.

Suggested Add-On Resource for the Trial Readiness Binder

Based on site feedback, this document may be strengthened further by creating a short companion resource such as:

Angelman Syndrome: What Every Staff Member Should Know

A one-page or two-page quick reference for:

- PACU nurses
- OR staff
- Anesthesia teams
- Front desk staff
- Transporters
- EEG or imaging staff
- Rotating inpatient or procedural staff

This could include:

- Common Angelman behaviors and communication differences
- Sensory considerations and triggers
- Tips for successful interaction
- Things to avoid
- Questions to ask parents
- Reminders that parents are the best source of calming and communication strategies
- A brief note on chronological age versus cognitive/functional presentation

Part 5:
Appendices

Part 5: Appendices

A. Glossary of Commonly Used Clinical Research Terms
B. Resources to Assist with Protocol Adherence — Tools and Templates
    1. Tools and Templates
C. External Resources for Key Members of the Research Team

Appendix A. Glossary of Commonly Used Clinical Research Terms

Commonly Used Clinical Research Terms

Excerpted from Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice

Adverse Drug Reaction (ADR): In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Regarding marketed medicinal products: a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Amendment (to the protocol): (See Protocol Amendment)

Applicable Regulatory Requirement(s): Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

Approval (in relation to Institutional Review Boards): The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

Audit: A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Audit Certificate: A declaration of confirmation by the auditor that an audit has taken place.

Audit Report: A written evaluation by the sponsor's auditor of the results of the audit.

Audit Trail: Documentation that allows reconstruction of the course of events.

Blinding/Masking: A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

Case Report Form (CRF): A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

Certified Copy: A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

Clinical Trial/Study: Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

Clinical Trial/Study Report: A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).

Comparator (Product): An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

Compliance (in relation to trials): Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

Confidentiality: Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

Contract: A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

Coordinating Committee: A committee that a sponsor may organize to coordinate the conduct of a multicentre trial.

Coordinating Investigator: An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.

Contract Research Organization (CRO): A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

Direct Access: Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

Documentation: All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

Essential Documents: Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see 8. Essential Documents for the Conduct of a Clinical Trial).

Good Clinical Practice (GCP): A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Independent Data-Monitoring Committee (IDMC): An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

Impartial Witness: A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

Independent Ethics Committee (IEC): An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favorable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Informed Consent: A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Inspection: The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

Institution (medical): Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

Institutional Review Board (IRB): An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Interim Clinical Trial/Study Report: A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

Investigational Product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Investigator: A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. (See also Sub Investigator).

Investigator/Institution: An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements".

Investigator's Brochure: A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

Legally Acceptable Representative: An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

Monitoring: The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Monitoring Plan: A document that describes the strategy, methods, responsibilities, and requirements for monitoring the trial.

Monitoring Report: A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs.

Multicenter Trial: A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

Nonclinical: Study Biomedical studies not performed on human subjects.

Opinion (in relation to Independent Ethics Committee): The judgement and/or the advice provided by an Independent Ethics Committee (IEC).

Original Medical Record: See Source Documents.

Protocol: A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.

Protocol Amendment: A written description of a change(s) to or formal clarification of a protocol.

Quality Assurance (QA): All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

Quality Control (QC): The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

Randomization: The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments to reduce bias.

Regulatory Authorities: Bodies having the power to regulate. In the ICH GCP Guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities.

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR): Any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Sponsor: An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Sponsor-Investigator: An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

Standard Operating Procedures (SOPs): Detailed, written instructions to achieve uniformity of the performance of a specific function.

Sub Investigator: Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). (See also Investigator).

Subject/Trial Subject: An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

Subject Identification Code: A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.

Trial Site: The location(s) where trial-related activities are conducted.

Unexpected Adverse Drug Reaction: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Validation of Computerized Systems: A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. The approach to validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.

Vulnerable Subjects: Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

Well-being (of the trial subjects): The physical and mental integrity of the subjects participating in a clinical trial.

Appendix B. Resources to Assist with Protocol Adherence

B.1. Tools and Templates

The tools listed within the following table were provided to assist with protocol adherence. These documents do not supersede those required by your facility or the sponsor; these tools should be considered an additional resource. The templates themselves have been obtained from a variety of sources as indicated within each document and the associated footnote.

The tools provided below are not requirements, but merely included as a potential resource which can be customized to meet the needs of each institution and protocol and to help you to optimize the collection and organization of required documentation throughout the clinical trial lifecycle. Additional information about similar tools and templates can be found in the appendices of our complementary toolkits for study coordinators and clinical evaluators.

Please note: If an FDA audit were to occur, all research staff must adhere to those SOPs that are implemented at your site. Routine internal audits and applicable staff training should be utilized to verify use.

Title	Tools, Templates, & SOPs
Adverse Event (AE) reporting	Adverse Event Log; Adverse Events Record Template; Safety Assessment and Reporting SOP
Audit / Quality Control	Self Audit SOP
Case Report Form	Case Report Form Template (Generic)
Activities for study close out	Study Close Out and Early Termination Checklist; Site Close Out SOP
Communication documents*	Meeting Minutes *Maintaining accurate, well-documented medication logs is an especially important part of recordkeeping.
Concomitant Medications	Concomitant Medications Log
Drug accountability and storage	Pharmacy Accountability Form; Managing Investigational Drug SOP
IND Safety Report	IND Safety Report Log
Informed consent process	Informed Consent Version Tracker; Informed Consent SOP
Protocol Deviation	Protocol Deviation Log
Screening & Enrollment	Recruitment and Enrollment SOP; Subject Screening Log; Subject Identification Log
Site Initiation	Site Initiation SOP
Staff Training and Study Handover	Staff Training and Study Handover SOP
Standard Operating Procedures (SOPs)	SOP for Preparing SOPs; SOP Template; SOP Management

Appendix C. External Resources for Key Members of the Research Team

Resources on AS, Genetic Disease, and Clinical Research Topics

This Appendix offers information about various training resources that may be of interest for research teams working on clinical trials for Angelman Syndrome (AS). In addition to the ASF website, ASF also maintains information for trainings; specifically for clinical research coordinators.

CLICK HERE for resources that could be useful for those in the medical community treating people with Angelman syndrome. You'll find published papers, articles, treatment guides, research studies and videos.

Resources on Genetic Diseases and Rare Diseases

PBS: The Gene: An Intimate History (Free)
A documentary series that discusses the history of the human genome and diagnosis and treatment of genetic diseases.
https://www.kpbs.org/news/2020/apr/06/gene-intimate-history/

Rare University Courses: Understanding Genetic Concepts and Drug Development (Free)
Global Genes has created two online courses that will be of interest for those new to rare disease clinical trials. The first, "Genetic Concepts for Rare Disease Patients and Families" is a series of over two dozen online lectures presented in four sections: genetic concepts, heredity and family, genetic testing, and scientific advances. The second, "Understanding Drug Development" reviews the drug development process; the roles of patients, funders, researchers, and regulators; steps in development and clinical evaluation; regulatory review; and considerations specific to rare diseases. Courses are free with a free account. Course Catalog - Rare University

Resources on Clinical Research Topics & Related Trainings

ACRP Resources (Cost varies; some resources are free)
The Association of Clinical Research Professionals (ACRP) has an array of training resources for entry level, intermediate, and senior clinical research professionals. For online resources, users of their website can sort resources based on role, knowledge level, contact hours (if continuing education credits are needed), type of resource, and competency area. Many trainings are free to members, although others require payment for both members and nonmembers. ACRP also offers periodic in-person meetings and training workshops.
https://acrpnet.org/training/

Transcelerate Multimedia Library (Free)
The Trancelerate video library offers videos on a variety of important and emerging issues in clinical research, which are free to view and may be of particular interest to those who want to learn about innovations in clinical research approaches.
https://transceleratebiopharmainc.com/video/

SOCRA ONLINE Educational Offerings for Clinical Research Education (Cost varies)
The Society of Clinical Research Associates (SOCRA) offers in-person and online training resources. Information about in-person meetings and training workshops can be found on the SOCRA website. Online courses are intended to provide access to training and continuing education that will promote quality clinical research, protect the welfare of research participants and improve global health. The courses focus on essential concepts in clinical research.

https://www.socra.org/conferences-and-education/online-courses/

CITI Program
Offers a wide range of key trainings for those involved in clinical research.
https://about.citiprogram.org/en/homepage/

Global Health Network
Includes a variety of free training opportunities, including short courses and modular courses. Certificate is provided upon completion of each course.
https://tghn.org/

NIH Training Center (NIH, n.d.)
Offers free training on ethical issues, roles and responsibilities of the institution and the investigator, regulatory issues and media. Welcome to the NIH Training Center | Office of Human Resources

HHS.gov
Provides a comprehensive overview of HIPAA and confidentiality issues.
https://www.hhs.gov/hipaa/for-professionals/special-topics/research/index.html

An Individual's Right to Access and Obtain Their Health Information Under HIPAA
FREE CME that reviews patient rights related to HIPAA.
https://www.medscape.org/viewarticle/876110?src=acdmpart_ocr-hhs_876110/

Other External Resources

- Coursera Courses and Specializations (Cost varies; some courses are free)
  - Coursera offers a wide range of courses in clinical research, drug development, and project management topics.
  - *www.coursera.org*
- EdX Courses, Programs, and Degrees (Cost varies; some courses are free)
  - EdX has a diverse set of courses, programs, and degrees in a large number of topics including data sciences, the life sciences, and physical sciences. EdX is both non-profit and open source.
  - *https://www.edx.org/*
- LinkedIn Learning (Requires account; some courses are free)
  - LinkedIn Learning offers an ever-growing array of courses. Some courses are free, while others require a subscription. https://www.linkedin.com/learning

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