Guidebook for **PARTICIPANT-FRIENDLY CLINICAL TRIALS** in **AUTISM**

for investigators, researchers, clinical trials staff, and the autism community

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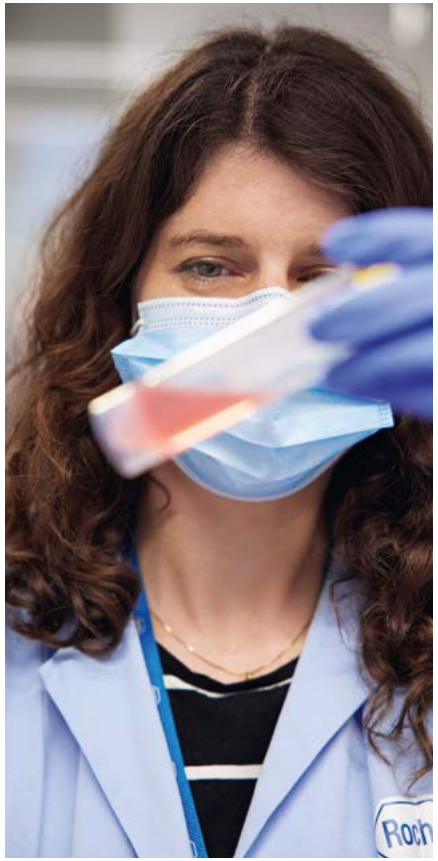
Contents



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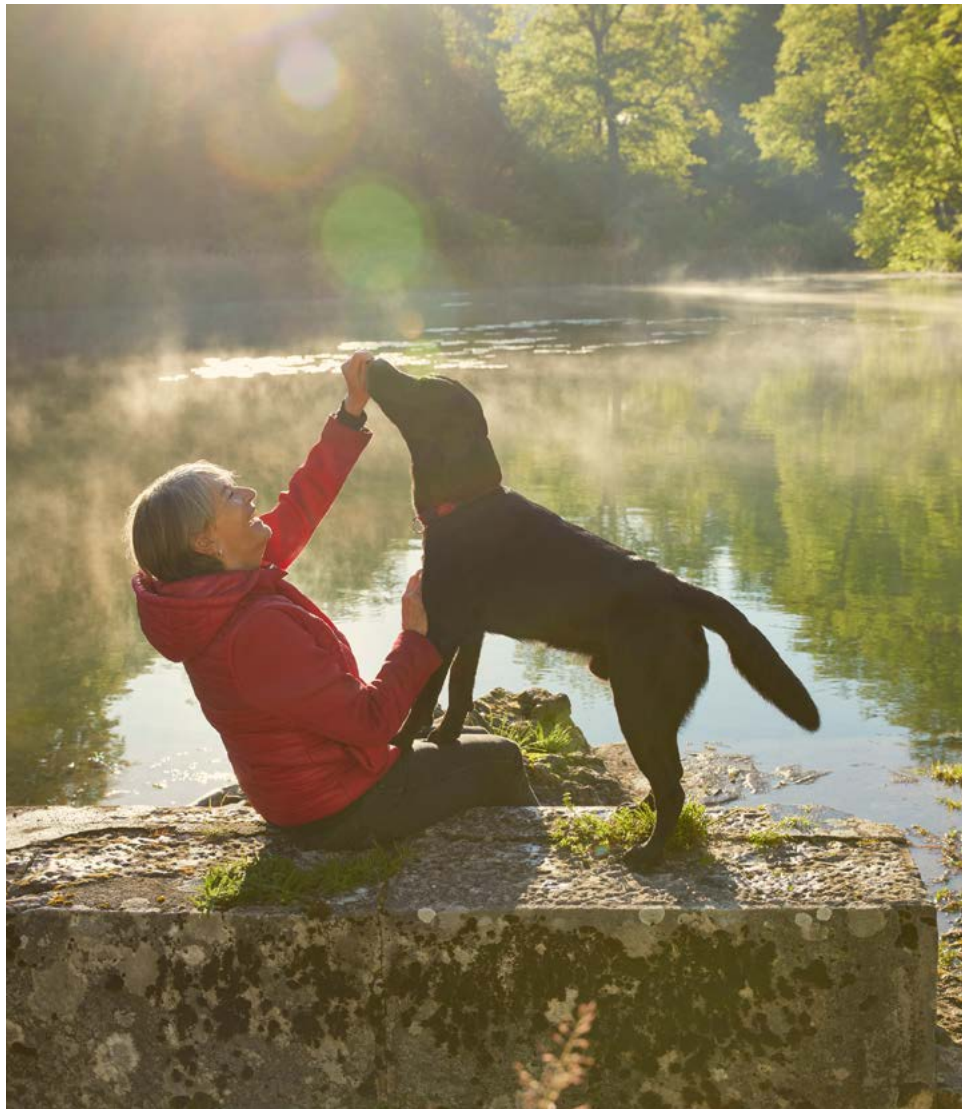

The Guidebook for Participant-Friendly Clinical Trials in Autism was co-created by Roche and The Clinical Trials in Autism Council. The Council received honoraria for their time as per local regulations, apart from in the cases of Autism Europe, Autism Science Foundation, and Autismo Burgos, who freely volunteered.

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This Clinical Trials Guidebook provides general considerations that will be relevant to all clinical trials in autism with the goal to make them participant-friendly, as well as specific caveats for paediatric, adult, profoundly autistic and lower support needs participants, and supporters. It does not include a comprehensive list of recommendations that will be possible for every type of clinical trial and is not a guarantee for meeting the mentioned goal.

Executive summary

The autism community is highly diverse, made up of autistic people and supporters of various ages, IQs, and levels of support needs. They face unique barriers to healthcare and struggle with access to care. Moreover, systemic, logistical, and historical concerns have resulted in suspicion from parts of the community towards the healthcare and pharmaceutical industries. Due to these factors, combined with the rigid design of clinical research, autism trials are generally not inclusive or autistic friendly.

In late 2021 and early 2022, Roche partnered with members of the autism community to develop a document to ensure that clinical trials meet the needs of autistic people and their supporters. This Guidebook for Participant-Friendly Clinical Trials in Autism aims to help investigators, researchers, clinical trials staff, and the autism community:

- better understand autistic people, their family members and supporters, their journeys, and the challenges traditionally faced in clinical research
- design, set up, recruit for, conduct, and follow-up after clinical trials in autism, including guidance on retention barriers and potential solutions
- improve the way that research is carried out in autism
- increase the inclusivity of non-autism trials to autistic participants and their supporters.

The Guidebook focuses on four stages of the clinical trial process: designing, recruiting, conducting, and post-trial activities. While there are many recommendations, both general and specific to sub-groups within the autism community (a more detailed overview can be found in the chapter summary for chapters 3, 4, 5, and 6), the following considerations were chosen as the most important for each section.

Key consideration before designing clinical trials

The ability to personalise the clinical trial experience to the extent possible and rapidly adapt to any feedback will be key success factors for any autism clinical trial.

Prioritised considerations

Designing clinical trials

1. Include members of the autism community (representing subgroups relevant to the clinical trial population) in the study design process.
2. Take every opportunity to reduce the number and frequency of assessments.
3. Choose endpoints that will be important based on participant age during the trial and for future life, such as those found in the World Health Organization Quality of Life Abbreviated Scale (WHOQOL-BREF), and those that reflect factors like self-sufficiency (living independently relevant to the individual's situation, socialising, autonomy etc.), employability, and self-injury.

Recruiting for clinical trials

1. Provide key information for participants and supporters at this stage, including:
   - who can participate (to set expectations)
   - the aims of the trial
   - the trial drug, its action, safety, and effectiveness
   - expected time and travel commitments
   - expected tests and measurements.
2. Recruit participants from a variety of cultural, socioeconomic, and ethnic backgrounds, and functional levels to represent the autism community as accurately as possible.
3. Provide the information in a variety of formats (print, visual, audio, and video) to increase accessibility.

Conducting clinical trials

1. Most concerns from participants and supporters stem from logistical issues, so tackling these will reduce dropouts (see Chapter 5a).
2. Offer an easily accessible 24/7 helpline for side effect advice and support while away from the trial site.
3. Building trust between trial staff and participants and supporters from the beginning is vital to a positive trial experience and reducing dropouts (see Chapter 5b).

After clinical trials

1. Provide clear and explicit information on whether there is an after-care package, what is included, what are the trial sponsors responsibilities in the package and how long after-care will be provided.
2. Offer an open-label extension when possible (Phase 2 and above).
3. Clearly summarise what the trial results mean for the autism community.

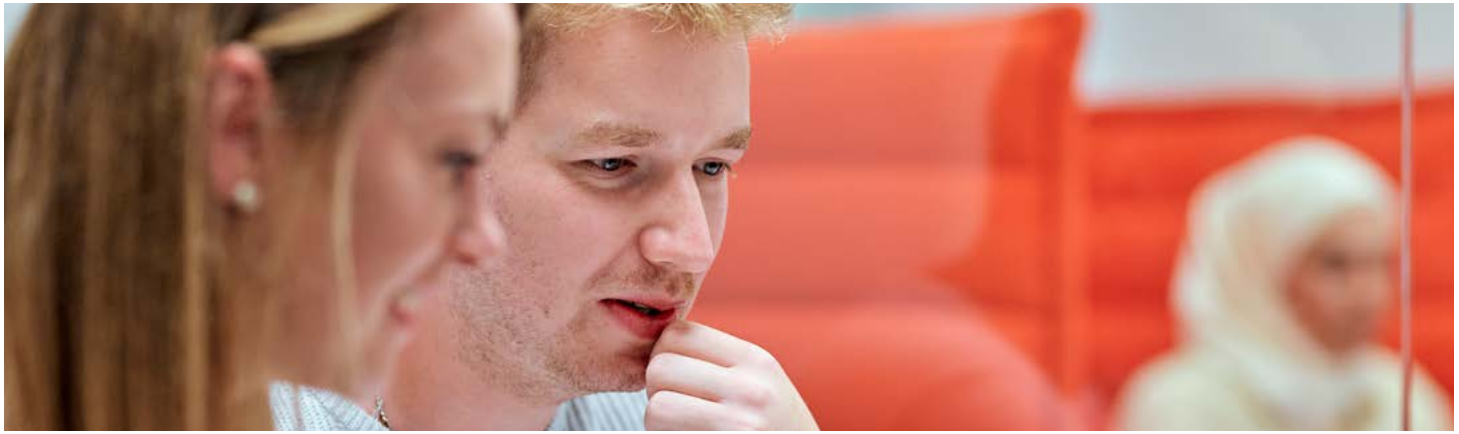
Fundamentally, the considerations found in this Guidebook aim to increase accessibility and participant-friendliness of autism clinical trials and help non-autism clinical trials to be more open to potential autistic participants.

Terminology

Correct language remains an area of debate amongst the autism community.[1-3] However, it is vital that appropriate terms are used to show respect.

This Guidebook has been co-created with autism community representatives to ensure that any terminology used is generally inclusive and autistic friendly. **The following avoided and suggested terms provide some guidance on language, however there is no right or wrong answer.** There will be significant variation in preferences depending on the individual, language, region, and culture. Always consult members of the local autism community during the trial design phase to ensure appropriate use of terminology.

Avoided terms	Suggested terms
Suffers from / sufferer of autism; Victim of autism; Autism spectrum disorder (ASD); Asperger's syndrome	**Autistic person, adult, child; Person / adult / child living with autism / profound autism; Person / adult / child with autism / profound autism**
Carer / Caregiver	**Supporter / Support person**
Autism symptoms	**Characteristics, traits, behaviours, features**
High / Low functioning	**Higher / Lower support needs, autism with co-occurring diagnoses (e.g., autism with / without intellectual disability)** • some materials refer to autistic people with higher support needs as having 'profound autism,' as per *The Lancet Commission on the future of care and clinical research in autism*[4]
Special needs	**Additional needs**



Introduction, objectives, and rationale

Welcome to The Guidebook for Participant-Friendly Clinical Trials in Autism

Representatives of The Clinical Trials in Autism Council and Roche have created this Guidebook. By building upon first-hand insights gathered by the autism community, this Guidebook aims to ensure that future studies are more participant-friendly with the goal of improved recruitment and retention within clinical trials.

The autism community expects collaboration with its members in the development of all clinical trials, autism or other, to hear their perspectives and gain input, and should not be an afterthought. Health authorities, health technology assessments, and payors acknowledge the importance and need to hear the expertise and perspectives of representatives of different conditions.[5] They already partner with them in a systematic way and integrate them into development and decision-making processes as the end users of any interventions, services, or supports. There is a strong focus on generating evidence that is relevant to those living with conditions. The only way to understand this is to engage with people who can represent communities so that the trials can be designed to generate this evidence.

Participating in a clinical trial can be a challenging experience. However, we can improve the overall trial experience, recruitment, and retention by identifying elements of trials that can be more participant-friendly and integrating those changes into trial design. Ultimately, this process contributes to the success of the study treatment and improves outcomes for autistic people.

How to use this Guidebook

Why?

This Guidebook aims to help ensure that clinical trials are accessible for, and meet the needs of, autistic people and their supporters. This will be achieved by providing a clear source of information for those who are designing or conducting clinical trial research in autism and non-autism trials with autistic participants, as well as members of the autism community who are interested in clinical trials.

What?

This document has been co-created by members of the autism community and Roche to increase accessibility and participant-friendliness of autism clinical trials and help non-autism clinical trials to be more open to potential autistic participants.

Who?

The content is aimed at researchers, industry members, patient advocacy groups, and the autism community to help them:

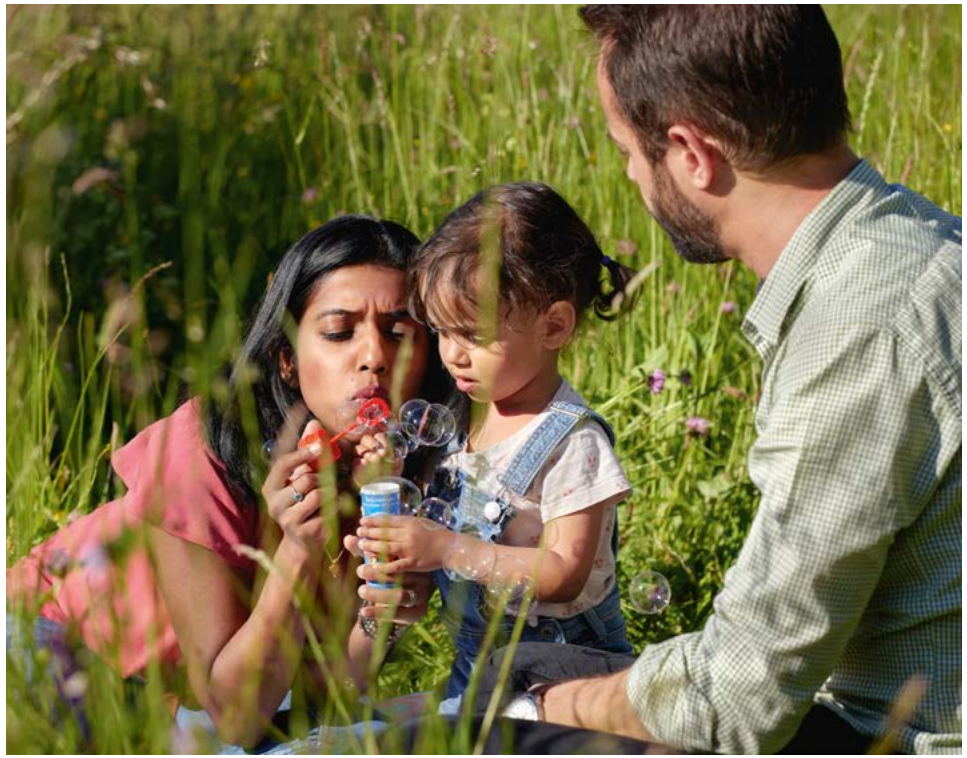
- better understand autistic people, their family members and supporters, their journeys, and the challenges traditionally faced in clinical research
- design, set up, recruit for, conduct, and follow-up after clinical trials in autism, including guidance on retention barriers and potential solutions
- improve the way that research is carried out in autism
- increase the inclusivity of non-autism trials to autistic participants and their supporters.

How?

Note:

- Definitions of key terms used throughout this Guidebook are provided on page 6.

Chapter 1:
Understanding autistic people, their family members and supporters, and their needs



Chapter summary

- The autism community is highly diverse, and needs vary based on age, gender, cognitive / language abilities, level of support needs, and numerous other individual and environmental factors.
- While differences in human minds are a biological fact, the Neurodiversity Paradigm remains a subject for debate amongst the autism community.[6]
- There is suspicion amongst some members of the autism community towards healthcare, research, and industry for a variety of reasons, including poor information on treatment and side effects, misdiagnosis, cost and stigma during care, longstanding barriers to clinical trials, and a lack of accurate endpoints.
- The Lancet has commissioned a set of recommendations for care, and importantly, clinical research in autism.[4]

Autism refers to a range of conditions that are characterised by childhood-onset challenges with social skills, repetitive and restrictive behaviours, speech, non-verbal communication, and sensory issues.[7-9] Despite being considered a common neurological condition (1 –2.5% prevalence in children), there has been little pharmacological advancement in the field.[10]

A key part to making clinical trials in autism accessible and participant-friendly is not only understanding the autism community and their journeys, but appreciating the challenges and barriers they have typically faced in the research process and from across the community itself.

1. Differences amongst the autism community

The autism community, made up of autistic people, their family, supporters, and advocates is highly diverse. The community includes autistic children, adolescents, and adults where the characteristics of individuals differ and are further separated by variations in factors such as IQ and language skills.[4] Broadly speaking, autistic people have either profound autism or lower support needs. However, this classification is not always accurate, as an autistic individual may have a high IQ but struggle with other aspects of life, like communication.[11]

Moreover, each of these groups face different social circumstances; education, living independently, working etc., which can change a person's support needs from one situation to another. Their family and supporters will naturally face different experiences and challenges too, which may result in many different opinions, motivations, and beliefs.[12]

Access is also a key factor that impacts the autism community in various ways. There are significant differences between high, middle, and low resourced countries regarding access to diagnosis and treatment and trials. Coverage can also change within countries depending on regional resourcing.

These differences across the community have resulted in inequalities in clinical research. For example, exclusion criteria have typically discounted those with profound autism from trials due to factors like IQ, associated characteristics, and taking other medications. In addition, research has often neglected autistic people from lower socioeconomic or ethnic minority backgrounds and autistic females. Moving forward, hearing all voices and increasing diversity are critical for autism research.

2. Neurodiversity

Neurodiversity refers to the biological fact that the human mind is limitlessly diverse.[13] For example, one individual may have poor organisational skills but show strong creative thinking.[11] Neurodiversity should not be confused with the Neurodiversity Paradigm, a perspective on neurodiversity, that there is no 'healthy' or 'unhealthy' type of brain or mind and that neurodiversity is like other forms of human diversity, such as gender or ethnicity.[13]

Parts of the autism community follow the Neurodiversity Paradigm, perceiving their neurodivergence, or that of their children, to be a strength. But this is not without controversy. For example, some parents of profoundly autistic children may only see a positive future for their child with some form of intervention or support.[14] These differences in opinion often shift enthusiasm for clinical trial participation across the community.

3. Suspicions from parts of the community towards healthcare, research, and industry

Despite significant increases in autism awareness and science in recent years, much more work is needed to improve the outcomes of autistic people and their supporters, as well as access to support.[3] This has resulted in suspicion from some members of the autism community, particularly those with lower support needs, towards healthcare, research, and the pharmaceutical industry. On the other hand, there is often less distrust in the profoundly autistic community due to a greater interest in and need for medication.

a) Frustrations with healthcare in general[9,15-20]

Many autistic people, ranging from children to adults, and their families, are let down by healthcare systems. Despite increased risk of other physical and mental health conditions, early mortality, and higher suicide rates, autistic people face more barriers to healthcare access than neurotypical people. These can include:

- very frequent misrecognition and late recognition of autism, which can be upsetting for autistic people and their supporters
- the cost of ongoing care in countries like the USA can be very expensive
    - Even countries with national healthcare systems often struggle to provide optimal care for autistic people
- prolonged pharmacological treatments for associated traits and comorbidities
- complex and time-limited healthcare systems with many different healthcare professionals (HCPs), medication regimens and administrative routes
    - There is also a lack of support when navigating healthcare systems, which the COVID-19 pandemic has disrupted further
    - Effective interventions often require a multidisciplinary approach, which can be challenging when HCPs work independently
- issues when reporting physical and emotional characteristics
- issues when communicating with HCPs, e.g., booking appointments or attending doctors' consultations virtually can be difficult for some autistic people (although this may be beneficial for some individuals)
- sensory sensitivities and difficulties in understanding situations and environments can make the entire healthcare experience off-putting for autistic people
    - These sensitivities can also prevent doctors from correctly assessing the individual, resulting in wrong conclusions being drawn
- stigma from HCPs who either assume how autistic people are feeling or have limited formal training for caring for autistic people.

Due to the issues stated above, some autistic people and their supporters may perceive little difference between healthcare and clinical research, and be automatically suspicious if approached by or recommended for a trial.

b) Perception of clinical trials

Despite the increased research in autism, perceptions of clinical trials from autistic people remain mixed. There are general barriers for participation in any clinical study, but autistic people and their supporters face specific obstacles.[21]

Barriers for autistic people include:[21]

- poor previous experiences with treatment
- ideological opposition to biomedical interventions for autism
- general day-to-day difficulties faced by those with profound autism and autistic children
- exclusion due to other medication or comorbidities
- low general awareness of clinical trials and sometimes negative perceptions, i.e., some autistic people link clinical trials to men in white coats and animal testing, or there may be a lack of understanding that not all clinical trials

involve testing of pharmacological treatments
- the logistical challenges of needing a support person to attend the trial site
- fear of side effects, particularly long term or mental health side effects like suicidality
- fear of drug interactions and having to stop medication that the individual is familiar with
- fear of what will happen after the clinical trial, e.g. the implications of having to stop taking a medication that had a positive impact once the trial is over
- anxiety of having blood taken or electrocardiograms (ECGs), electroencephalograms (EEGs), magnetic resonance imaging (MRI) conducted, etc.
- concerns around what will happen to data shared and transparency of the data sharing process.

Barriers for supporters include:[21]
- perceiving medication as a negative approach to treatment or reluctance to give their children medications
- lack of understanding of the clinical trial process, the high failure rate of trials, and poor communication of trials in the media and popular culture
- fears of risks, side effects, or giving the wrong kind of hope
- changes in routine and other medication
- travelling to and from clinical trial sites over a long period of time
- high numbers of physical, neurological, and psychological tests
- lack of transparency between supporters and trial staff and any breakdown in communication.

While there are also autistic people and supporters who would be willing to participate in a clinical trial, many are not approached by researchers or are unsure how they would get involved.[12] Often trials are conducted at specific trial centres, which decreases accessibility for many people due to a long commute.

C) Endpoints in research

There continues to be little agreement on endpoints for clinical trials in autism in general, but with prominent knowledge gaps for adult measures.[10] Expert reviews from 2014-2015 found that no core characteristic endpoint measures met the highest standard for endorsement, including those for social communication and restrictive and repetitive behaviours.[10]

Clinician- and supporter-related measures are still widely used, which adds to the debate. These can cause frustration for autistic adults / those with low support needs who may feel disempowered during the trial process. However, there may be few alternatives, and the perspectives of supporters are still valued and meaningful in autism research.

D) Perception of industry[6,20-24]

Historically, there has been some mistrust from parts of the autism community towards the pharmaceutical industry. This possibly stems from various sources, including:
- some members of the autism community being fundamentally opposed to the goals of industry
- previous inappropriate research objectives
- previous off-label prescription of medication to parts of the autism community
- continuing hesitancy and discussion around the anti-vaccine / 'vaccines cause autism' movement, which has once again been brought to the forefront following the COVID-19 pandemic and vaccination programme
- fringe practitioners who promise miracle treatments / cures for autism and often appeal to 'big pharma' conspiracy theories about suppression of falsely effective treatments
- criticism and fear of eugenics because of genetic research that lacks transparency or dialogue with the community.

However, opinions are changing and reflect the different attitudes within the community. As more research has been conducted into the neuroscience behind autism, the targets of future medicines have become clearer, which is alleviating some concerns of autistic people and their supporters. Moreover, trials are being redesigned to be 'gene-first', improving success rates with more homogenous groups of participants, rather than recruitment of anyone with autism regardless of severity or genetic cause.

In conclusion:

There is a clear need for meaningful change in both care and research in autism. The Lancet has commissioned a set of recommendations with that aim in mind.[4] Of relevance to this Guidebook is the proposal to include members of the autism community in the clinical trial design process and ensure that research correctly communicates its aims and focuses on improving the quality of life (QoL) of autistic people and their supporters.

Chapter 2:
Autistic person and supporter journeys

Chapter summary

The journey of an autistic person through childhood, adolescence and into adulthood, as well as of their supporter, is highly diverse, with many different potential phases and challenges. Dr Stephen Shore famously wrote that:

"If you've met one person with autism, you've met one person with autism."

The following journey aims to gather the general stages and emotions that most autistic people and their supporters will face. Its purpose is to help give some understanding of the motivators, barriers, and feelings of potential participants and supporters in autism clinical trials.

Autistic individual's experience

Childhood (Birth to approximately 12-years)

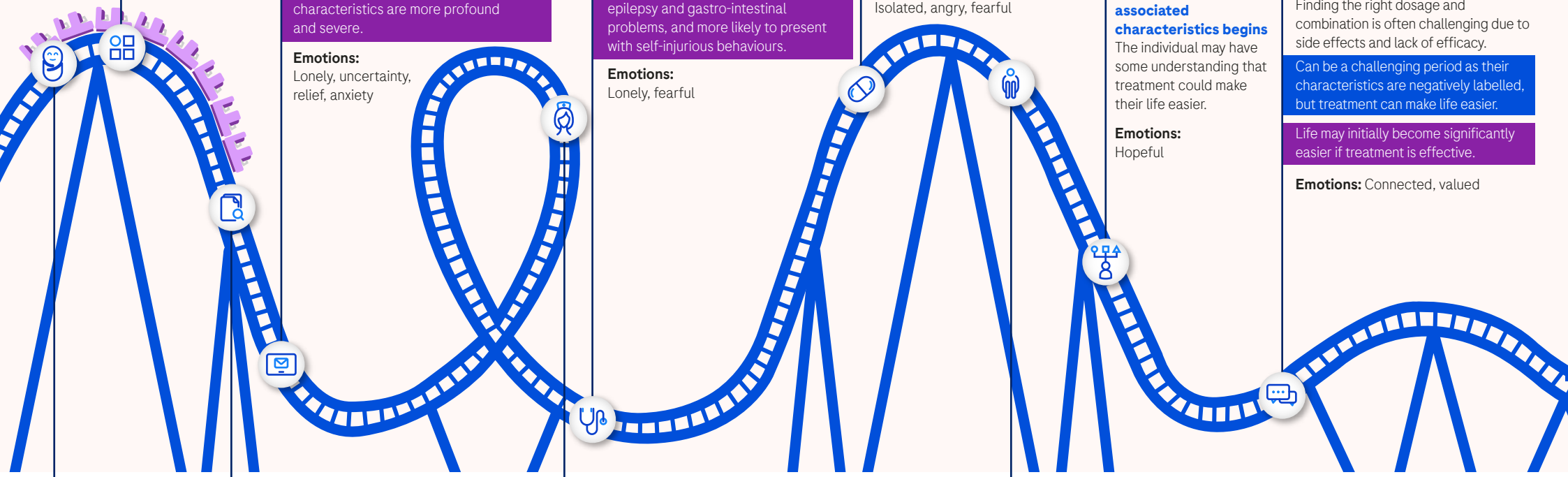
Key:

- Lower support needs
- Profoundly autistic

These two subtypes of autism are broad and generally subjective terms, and autistic people have a range of abilities and support needs that may or may not be captured by one of these terms.

This journey also relates to those who will at some point choose to have or require medication, and will not be relevant to every autistic person or their supporter's journey.

The roller-coaster represents a journey that is complex with many stages that will be positive for some, negative for others, or have both positive and negative emotions attached. Moreover, emotions are often not directly reported by the autistic individual, making it very difficult to truly understand a person's feelings at any stage. The point at which each stage is placed on the roller-coaster does not necessarily reflect the emotions felt at this stage.



Birth

Awareness of something different

Emotions:
Confused, lonely, sad

Diagnosis

May not be diagnosed until adolescence or adulthood. Characteristics may be mistaken for a normal part of 'growing up'. In some cases, the subtlety of characteristics can make recognition a lengthy process.

Typically diagnosed earlier as characteristics are more profound and severe.

Emotions:
Lonely, uncertainty, relief, anxiety

Testing

Testing is tricky for the individual with many visits to scary hospitals and clinics.

Emotions:
Confused, fearful

Introduced to treatment

Developing alongside peers.

Has issues with social integration, communication, concentration, or managing emotions.

Struggling to obtain critical life skills, like speech and autonomy. Often struggles with other comorbidities, like epilepsy and gastro-intestinal problems, and more likely to present with self-injurious behaviours.

Emotions:
Lonely, fearful

Discussions with healthcare professionals

Exhausting and seemingly endless explanations.

Lack of support to handle these discussions and subsequent feelings.

Emotions:
Overwhelmed, scared, unvalued opinions

Need for medication

Some aggression, social, communication, emotional, and concentration difficulties may hinder education somewhat.

Violent outbursts can be very disruptive, and difficulties with communication make it hard to express oneself.

Emotions:
Isolated, angry, fearful

Medication for associated characteristics begins

The individual may have some understanding that treatment could make their life easier.

Emotions:
Hopeful

Social isolation

Realises they are different, but struggles less with their behaviour, communication, concentration, and emotions so can cope better in traditional social settings. May still struggle with bullying or inability to make many friendships.

Realises they are different from others but reduced self-awareness, intellectual impairment, and inability to communicate can make it difficult to voice this. Often spoken for by supporters. Violent outbursts and frustrations have excluded them from many social situations.

Emotions:
Rejected, isolated, angry

New normal

Depending on the intervention, highly varied improvement in the frequency and intensity of behaviours such as anxiety, irritability, tantrums, aggressive behaviour, depression, obsessive-compulsive behaviours, hyperactivity.

Finding the right dosage and combination is often challenging due to side effects and lack of efficacy.

Can be a challenging period as their characteristics are negatively labelled, but treatment can make life easier.

Life may initially become significantly easier if treatment is effective.

Emotions: Connected, valued

Autistic individual's experience

Adolescence + adulthood (approximately 13-years and older)

Key:

- Lower support needs
- Profoundly autistic

Side effects of taking new medications after diagnosis or re-emergence of problem behaviours

Side effects can be scary and significantly impact an individual's routine.

Behaviours that were once under some level of control now reappear.

Emotions:
Uncomfortable, lonely, confused, distressed

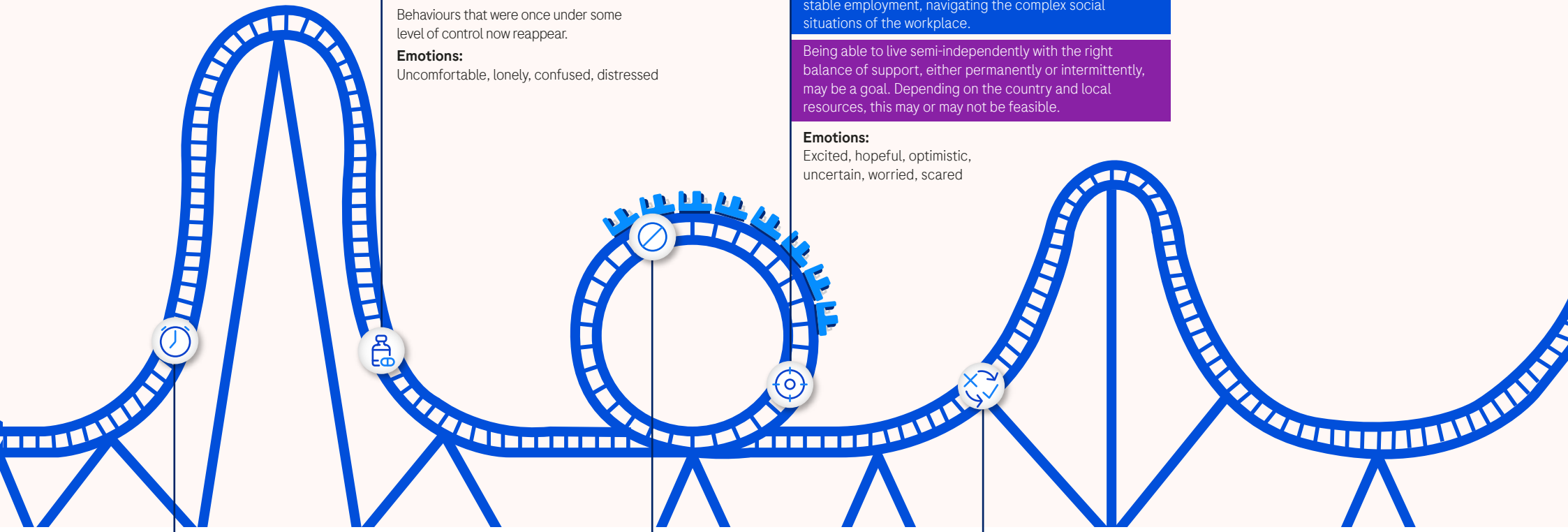
Goals change

Independence is the goal, but may be unsure how to achieve it.

Independence goals may be independent living, driving and using public transportation independently, finding stable employment, navigating the complex social situations of the workplace.

Being able to live semi-independently with the right balance of support, either permanently or intermittently, may be a goal. Depending on the country and local resources, this may or may not be feasible.

Emotions:
Excited, hopeful, optimistic, uncertain, worried, scared



Late diagnosis (in adolescence and adulthood)

Often a period of self-reflection after many years of feeling different and isolated.

Disproportionately common in women.

This can cause some anxiety if the person is planning or expecting parenthood due to fears that they may pass autism to their child.

Emotions:
Relieved, unsure

Education ends and access to care is limited

Feelings of uncertainty for what the future may hold.

Emotions:
Unsure, worried, fearful

Reframing can't to can

Mindset changes as the autistic individual begins to see their characteristics as positive skills, rather than negative weaknesses, attaining a better feeling of mastering one's situation.

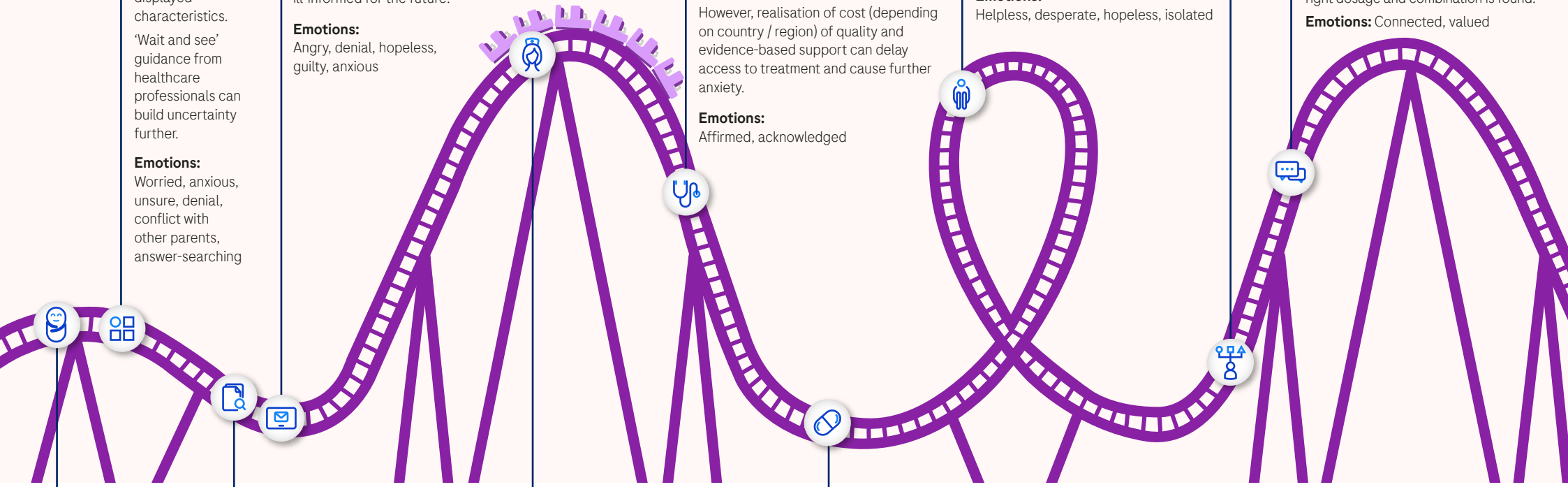
Finding the right level of social and work exertion takes time but is extremely important.

Emotions:
Relieved, uncertain

Supporter's experience
Childhood

Key:

- Lower support needs
- Profoundly autistic



Birth
The child brings much expectation of a happy life.

Emotions:
Hope, excitement, joy

Awareness of something different
Confusion around what is causing the displayed characteristics.

'Wait and see' guidance from healthcare professionals can build uncertainty further.

Emotions:
Worried, anxious, unsure, denial, conflict with other parents, answer-searching

Testing
Numerous tests and referrals to different specialists can be challenging and anxiety-inducing. Long waiting lists can exacerbate this. Some supporters find their concerns dismissed or that they're blamed for their child's behaviour.

Emotions:
Worried, anxious, apprehensive, overwhelmed

Diagnosis
Recognising a child as autistic can be overwhelming and shocking. Supporters often feel unprepared or ill-informed for the future.

Emotions:
Angry, denial, hopeless, guilty, anxious

Discussions with healthcare professionals
Trust is put in healthcare professionals who may offer a variety of strategies. Other specialists, such as psychologists and social workers, may now become involved, as well as peer support groups.

Struggle to coordinate between school and healthcare systems and fight for the right support for their child.

Emotions:
Hopeful, unvalued opinions, despair

Introduced to treatment
Begin to relax after the 'grieving' process as more management options are offered for core autism traits, such as:

- early intensive behavioural intervention
- applied behavioural analysis
- pivotal response treatment
- discrete trial teaching
- speech therapy.

And for associated characteristics, such as:

- occupational therapy
- physical therapy
- speech therapy
- medication.

However, realisation of cost (depending on country / region) of quality and evidence-based support can delay access to treatment and cause further anxiety.

Emotions:
Affirmed, acknowledged

Need for medication
Medication is typically seen as a last resort and needs long consideration of benefits and risks. Parents are often exhausted after trying every other available environmental and interventional solutions. Underlying conditions that require medication, such as gastrointestinal problems, may be masked by challenging behaviour.

Choosing medication is more challenging – there are fears that medication will change their child.

Choosing medication may be easier as the severe behaviour issues are highly troublesome and worrying.

Emotions: Helpless, secluded

Social isolation
Supporters may feel guilty or ashamed throughout the journey, despite support from healthcare professionals and the community.

Levels of isolation are higher as characteristics are more profound, causing supporters to avoid essential activities, like sports and exercise, or leisure activities, like meeting friends or going on holiday.

Emotions:
Helpless, desperate, hopeless, isolated

Medication for associated characteristics begins
Once initiated, any treatment concerns will either be reduced or exacerbated depending on the incidence of adverse effects or lack of expected effectiveness.

Emotions:
Hopeful

New normal
Supporters feel a sense of accomplishment once routines / habits become established and daily life becomes easier (if treatment is effective). However, it can take some time before the right dosage and combination is found.

Emotions: Connected, valued

Supporter's experience
Adolescence + adulthood

Key:

Lower support needs

Profoundly autistic

Side effects of taking new medications after diagnosis or re-emergence of problem behaviours
Can feel like a major disaster when side effects or relapse occur. Sometimes results in a loss of trust with healthcare.

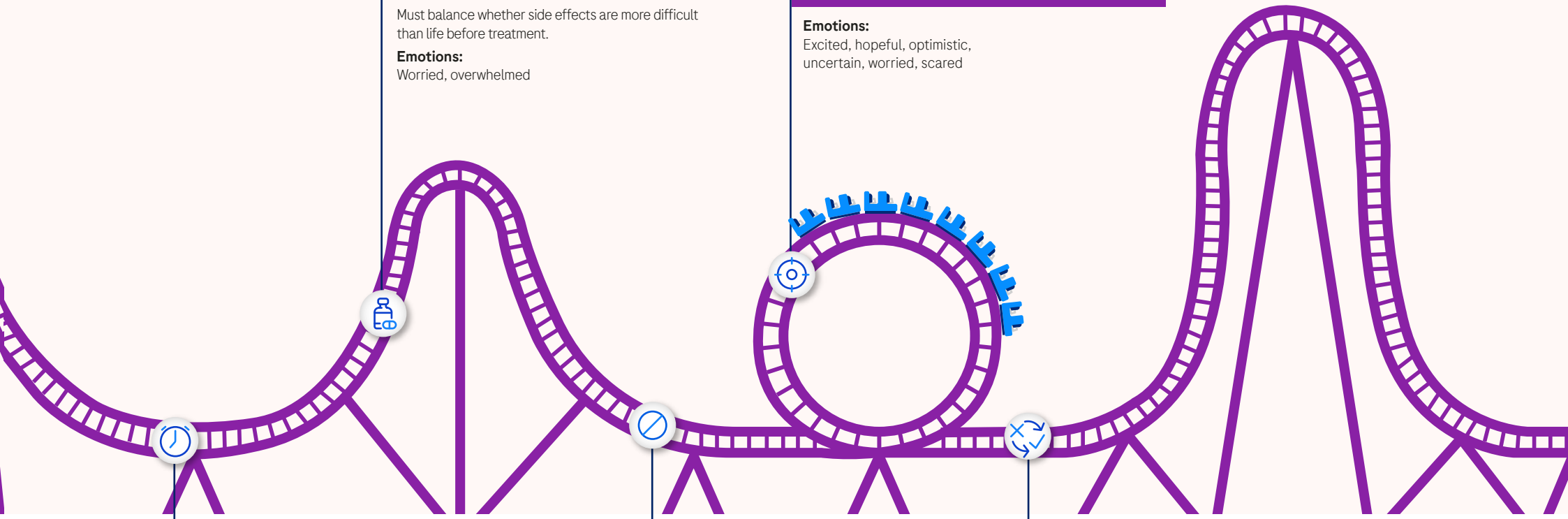
Must balance whether side effects are more difficult than life before treatment.

Emotions:
Worried, overwhelmed

Goals change
The goal is now to help the autistic individual achieve some level of independence.

Fears grow around what will happen to the autistic individual once the supporter can no longer provide care, such as during advanced age, illness, or after death.

Emotions:
Excited, hopeful, optimistic, uncertain, worried, scared



Late diagnosis (in adolescence and adulthood)
Can be a relief that they finally have an answer after all the years, but it can also cause anger towards healthcare professionals who 'ignored' their calls for a diagnosis and support.

Emotions:
Relieved, angry, unsure

Education ends and access to care is limited
As much external support is now taken away, it is down to the supporter to take charge of this role.

Particularly costly and time-consuming for supporters of profoundly autistic individuals who must now fill the gaps left by a lack of education, or find alternative day-care / respite services.

Emotions:
Unsure, worried, fearful

Reframing can't to can

Chapter 3:
Considerations when designing clinical trials

Key consideration before designing clinical trials

Due to the unique and varied nature of the autistic community, there is an important caveat to the considerations found in this Guidebook:

No single approach to clinical trials will be accessible for every autistic person and their supporters. The ability to personalise the clinical trial experience to the extent possible and rapidly adapt to feedback will be key success factors for any study in autism.

Therefore, the following chapters provide general considerations for autism clinical trial organisers, as well as some important specific considerations for paediatrics, adults, those with lower support needs, profound autism participants, and their supporters.

Chapter summary

- Include representatives of the autism community (specifically those representing groups relevant to the specific clinical trial population) in the study design process and ensure they are representative of different ages, genders, ethnicities, and backgrounds.
- Be aware of the differences in autistic people when deciding on inclusion and exclusion criteria, focusing on the individual biology and needs of participants.
- Consider diversity in the study population, e.g., include more profoundly autistic participants, different genders, and people from diverse backgrounds and ethnicities in trials, as they are often underrepresented in research with potentially the greatest need for support.
- Plan literal and inclusive communication of the purpose of the trial, the safety and effectiveness of the study drug, and the study agenda, including all the required tests.
- Design all participant-facing materials with the autism community.
- Keep the trial and trial visits as short as possible, considering how the length will impact participants and supporters.
- Provide a clear and understandable informed consent form (ICF), and explain any differences between participant and supporter documents.
- Aim for endpoints that show meaningful improvements in QoL or other outcomes relevant to the participants' daily lives, in addition to enhancements in core autism characteristics.
- Take every opportunity to reduce the number and frequency of tests (conduct remote monitoring / visits where possible) and justify any required tests.
- Site selection is crucial to ensuring participants have a positive experience.

a. Co-creation from the beginning

Fundamentally, autistic people and their supporters know what motivates and discourages them from participating in clinical trials. Therefore, include them in the study design process to deliver better outcomes for clinical trial participants.

General considerations

Include expert autism community representatives* early in the design phase so they can actively influence planning, not after decisions have been made.

Invite a diverse range of people from the community (potential participants and supporters) to provide their expertise in discussions to build a varied trial that is more accessible. However, ensure you invite those who will be relevant to your trial.

- I.e., if the trial will include participants with lower support needs, the views of profoundly autistic participants and supporters may not be valid.

Specific consideration
Consider representatives who have lived experiences relevant to the specific autistic sub-populations included in the trial, such as different age groups (toddlers, children, adolescents, and adults), those with lower support needs and profound autism, different ethnic groups, different genders, different socioeconomic groups, different IQ levels, verbal vs. non-verbal etc.

Work closely with participants and supporters to understand and co-create solutions that improve the paradigm of clinical trials and deliver better outcomes.

Listen to their needs carefully and consider solutions for these.

Specific consideration
Listen to the needs of each individual participant and supporter, and the whole group, to consider some of the most important challenges faced by the community:

- How does the participant experience life with autism?
- What path(s) do they follow to seek optimal care?
- What outcomes do they expect from clinical trials or new innovations in the field?
- What outcomes do they prioritise over others?
- What gap / hurdles does the participant face? e.g., daily living struggles, access to care, information / awareness, health policy issues.
- Where do they seek information about clinical trials?
- What role does their supporter play in their care?

Hold meetings at different stages throughout the design process to continuously reflect, question, and revalidate the design. If you cannot implement criteria as suggested, it is important to explain why, keeping a transparent dialogue with participants and their supporters.

Specific consideration
Ensure meetings are accessible, particularly for non-verbal attendees.

- Provide a non-verbal feedback system.
- Provide different communication platforms that can collect insights outside designated meetings i.e., chat box, polls, email, telephone etc.
- Offer a translator (for different languages and to help articulate sentences).
- Let the representative choose their individual form of communication.

Take the time to go into the details about the clinical trial design with potential participants and their supporters, however small the detail may seem. These insights can be important as they may result in a change of process, and can make a significant difference to participants and supporters.

- This includes items such as explaining what the schedule of assessments will be, how many visits are required, duration of visits, and whether they are at the site or done at home / virtually.
- An example would be the number of blood tests and how long each test will take to see if the request is realistic. Necessary tests can then be prioritised using this information.

Given that inclusion / exclusion criteria are vital for success of the study, discuss these with members of the autism community upfront to identify any potential recruitment issues and adapt in time.

Invite representatives from the autism community to sit on the study team during the design stage and throughout.

**Autism community representatives refers to any individual within the autism community, autistic people and their supporters, and autism organisation representatives who are able to contribute in co-creation discussions.*

b. Study population*

As previously mentioned, the autism population is highly diverse. This means that trials must have some flexibility and adaptability embedded from the beginning.

General considerations

Reflect on the different characteristics within typical participant populations.

Specific consideration
Be aware of differences, such as high IQ vs. low IQ, verbal vs. non-verbal, various associated characteristics etc.

Inclusion and exclusion criteria should be sensitive to possible differences in characteristics, with a focus on the individual biology and needs of participants.

Specific consideration

- Consider stratifying factors, like IQ, within the study to include a more diverse population and get more specific data at a sub-group level.
- Some autistic people require other medication for associated characteristics or have co-occurring conditions that may typically exclude them from trials.
    - Different ethnicities or support needs may have a higher prevalence of associated characteristics or co-occurring conditions, so review inclusion and exclusion criteria to include underrepresented groups.

Consider using the International Classification Form for ASD (ICF-ASD) to better understand and categorise participants with complex functional experiences.[25]

Regardless of the level of support needed, recommend that all participants bring a supporter with them in the trial (a family member or close friend), as this can help participants navigate the complexities and stresses of clinical research.

The informed consent form (ICF) should clearly define the role of the supporter in the clinical trial. The role of the supporter can vary per study, but consider also adding different scales, participant-reported outcomes (PROs), observer-reported outcomes (OBsROs) and proxy PROs to bring in a distinct perspective on the outcomes.

Specific consideration
Autistic adults with lower support needs may live alone and not have a traditional supporter, like a parent, available.

**While there are many barriers for inclusive research in autism, most come from widely held beliefs, such as poor compliance amongst autistic people, variations in characteristics, and a lack of treatment response. This has resulted in clinical trials favouring participants with lower support needs, despite a large proportion of the autistic population having profound autism, who in many cases have the greatest need for support. It is an important future step for research to include a broader range of autistic people, particularly those with profound autism and their supporters.*

c. Communication standards

Good communication is vital as it shows participants and their supporters that the trial organisers respect and care for them. Specific considerations must be made to ensure that both autistic participants and their supporters understand the trial without feeling stigmatised. For example, some autistic people will struggle to comprehend metaphors or non-literal statements.

The three principles of good communication that matter most in clinical trials are honesty, transparency, and clarity, and these are especially important to autistic people and their supporters.

General considerations

Ensure that any participant-facing materials (e.g., consent forms, fact sheets etc.) have input from community representatives.

Specific consideration
Gain input from representatives relevant to the study, i.e. profoundly autistic individuals and their supporters.

Select a site that has experience communicating with autistic participants and their supporters and can adapt its communications to individual participants and supporters throughout the trial.

Train trial staff to understand the perspectives of different participants and their supporters. Some participants may respond better to humour whereas others will require communication in a clear and literal way. Importantly, trial staff should be able to adapt to the communication preferences of the participants.

- Train staff to use the active voice and avoid double negatives. E.g. “you will then answer several questions in the questionnaires” vs. “several questions from a questionnaire will then be answered”, or “you should inform the study coordinator if you cannot attend an appointment” vs. “you should not not attend an appointment without informing the study coordinator”.
- Avoid the use of jokes or irony, unless the participant responds well to this.
- Keep conversational or ‘small talk’ to a minimum.

Specific consideration
Depending upon the trial, staff should receive specific training in communicating with autistic children and adults, those with lower support needs and profound autism, verbal vs.

non-verbal, and supporters.

Trial staff should also be prepared for challenging behaviours and aggression, with the correct protocol and training in place, especially when participants include children and those with profound autism.

Clearly discuss the purpose of the trial upfront using literal language and explain how it will benefit members of the autism community.

- Define terms such as open-label, blinded, Phase I-III.
- Explain why it is important to comply with the study and collect data as per the study protocol.

This will support trust building and help to set expectations of what is to come.

If including a placebo arm, participants and supporters should receive upfront information on what a placebo is, the 'placebo effect', and what will happen after the trial, i.e., open label extension where all participants receive the active drug.

Clearly communicate the safety and risks of participating in the clinical trial, as well as the benefits, using accessible means.

Collaborate with the community to review messaging and get this right.

Provide a clear and structured timeline of trial expectations, including when participants will need to be on site or a specific test or assessment will be conducted, so there are no surprises.

Ensure that participants and supporters understand beforehand why certain procedures, such as on-site visits, can only occur on certain days (visit windows) of the trial (e.g. on days 7-10 and not day 11).

Identify which stages of the trial would require further information (i.e., suicidality measures) and develop materials in a variety of formats to increase accessibility.

- Always avoid using slang, jargon, and medical terminology.

Specific consideration
Due to diversity in the autistic population, you should always develop communications in a variety of formats, such as print, visual print, films, and audio, to allow for differences in how communication takes place, ensure that information is inclusive, and that aspects of the trial are well understood.

Identify at which stages there is likely to be confusion between the participant and their supporter (i.e., dose escalation) and inform both parties early so they can anticipate these moments.

Describe all assessments or tests and why they are important to the trial.

Ensure there is clear communication around expectations and prepare this in advance; for example, some participants may not meet the inclusion criteria and it is important that they understand clearly why they are unable to participate on this occasion so as to not deter them from future trials.

Clarify and clearly define the role of the supporter in the study.

Correctly translate all materials for your required setting and ensure that local languages are included to be inclusive for minority groups.

d. Length of study and timelines

Generally, the longer a clinical trial takes, the greater the number of dropouts. This effect may be more exaggerated in autistic participants and their supporters.

General considerations

Keep the trial as short as possible.*

Justify the length of a trial with well communicated rationale.

Consider the impact of trial length on participants and supporters.

Specific consideration
Lengthy trials may disrupt important social interaction and early education during nursery and school, so consider conducting trials in evenings, on weekends or over holiday periods.

Offer compensation for lost earnings if trials take up considerable time during the working day (as per local compliance regulations).

**Exceptions are when outcome measures, such as the Vineland Adaptive Behaviour Scale,[26] will not show a meaningful change in a trial under 6-weeks long and behavioural trials where new tools are used, as participants may require more time to learn how to use the equipment.*

e. Informed consent form (ICF)

The ICF is an extremely important document, but it can be a source of confusion for participants and supporters. Because it contains a lot of important legal information, getting it right is a critical step to setting the tone for the entire clinical trial. It is also key that participants understand the inclusion and exclusion criteria of their trial and that all legal requirements are met at the same time. Co-create the ICF with members of the autism community to ensure participants and supporters will understand it.

General considerations

Consider the ICF process as a whole and how best to adapt this to support participants, rather than only the wording / format of the documents themselves.

ICFs are typically large documents due to the large amount of legal documentation required, so they should be broken down into bite-size sections.

Information that is especially important to participants and supporters, such as safety and efficacy data, should be provided in an easy-to-read format and / or broken down in a short executive summary for lay readers.

Specific consideration
Consider offering the ICF in a variety of formats (print, images / infographics, pictograms, audio, and video) to aid readership of different participants.

ICFs for participants may need to be adjusted compared to those given to supporters to increase accessibility, however this must be clearly explained.

- Participants or supporters may question the trustworthiness of the trial if differences are not explained.

Consider consent and assent issues for children and / or individuals who legally cannot give consent.

Specific consideration
It is good practice to consult the autistic child and obtain assent (whether this is appropriate should be judged based on the child's age, development, and understanding).

If assent is not appropriate, researchers should ask the supporter to monitor the participant throughout the trial and judge whether they are still happy to contribute. Researchers should follow local rules and laws for adults who are unable to consent.

Be aware that informed consent based on substituted decision-making is not compliant with the UN Convention on the Rights of People with Disabilities,[27] so it is important to promote supported decision-making whenever possible.

f. Outcome measurements*

Research has historically struggled to find accurate and reliable measures in autism, but most autistic people and supporters value endpoints and measurements that will be meaningful to their future lives. The challenge is that the huge variation in core characteristics and resulting behaviours means that endpoints will matter differently to individuals. It is important that the autism community can contribute in selecting the most relevant measures for any given study.

General considerations

Choose endpoints that will be important based on participant age during the trial and for future life, such as those found in the World Health Organization Quality of Life Abbreviated Scale (WHOQOL-BREF),[28] and those that reflect factors like self-sufficiency (living independently relevant to the individual's situation, socialising, autonomy etc.), employability, and self-injury.

Specific consideration
What a meaningful endpoint is will differ depending on age, gender, level of support needs, background, and region.

Consider using more personalised measures that better meet the needs of the participants (e.g., Goal Attainment Scaling [GAS]) and ensure these are validated.[29]

Specific consideration
GAS is one method to measure individual goals. Supporters may need to provide these goals for profoundly autistic participants, but some lower support needs participants may wish to be solely responsible for deciding these goals or involved in selecting some of them.

- Consider discussing any goals with participants and supporters together, regardless of level of support needs.

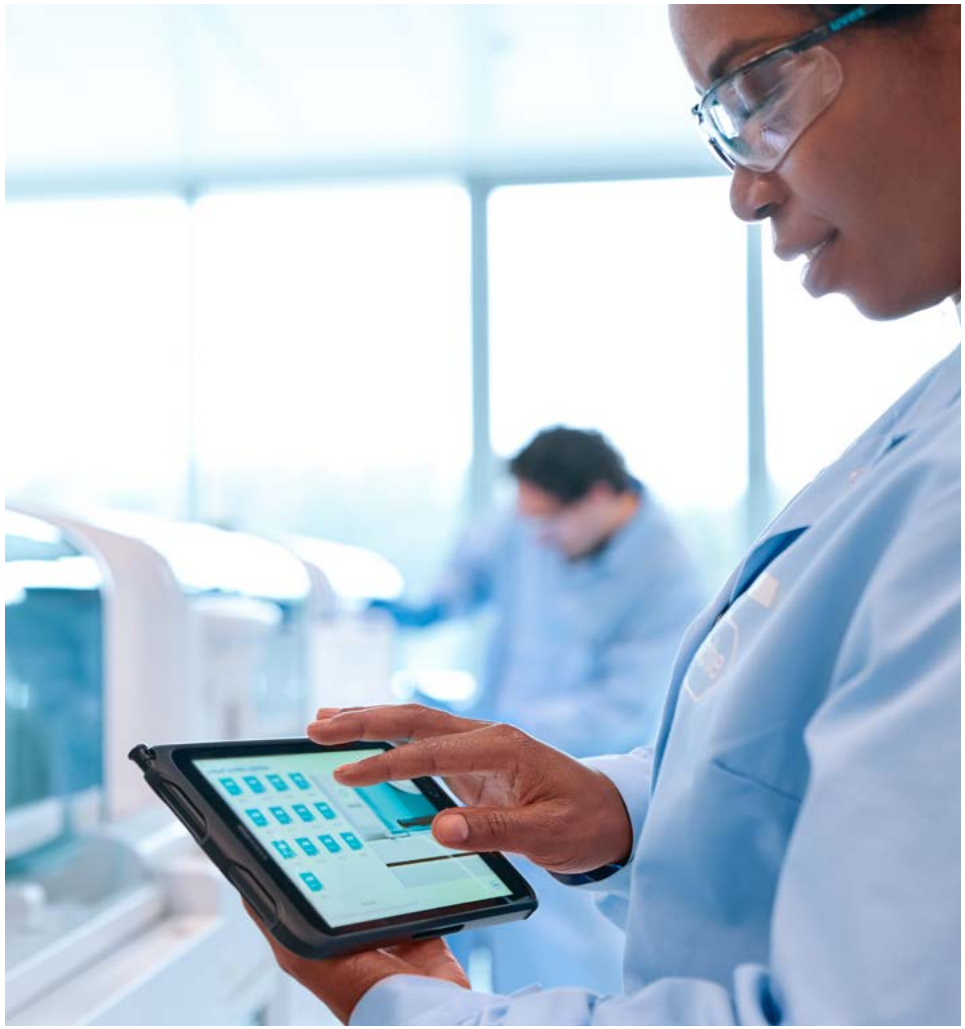
QoL should be measured as a primary endpoint in all trials.

QoL can be difficult to assess as a primary endpoint due to the broad range of concepts included in traditional scales. However, functional endpoints, can aid with measurement of concepts that relate to QoL.

Specific consideration
Consider using PROs, such as the PROMIS® Autism Battery, which can measure QoL across individuals of different ages.[30]

Blinded trial staff should administer outcome measures whenever possible.

Digital biomarkers, which can include active tests (memory, communication etc.), PROs and supporter-reported outcomes and passive monitoring (heart rate, sleep), may be a beneficial outcome measurement.†



**The Lancet Commission on the future of care and clinical research in autism highlights the need for more standardised measures, which are both meaningful and sensitive to changes in core characteristics and that can be compared across treatments.[4]*

† There is a great need for biomarkers in autism clinical trials for stratification of heterogenous participants into distinct study groups and to show efficacy of the intervention, for example. However, there is still much work to be done to identify biological markers. Digital biomarkers show promise, and it is likely that biomarkers in general will play a key role in future clinical research.

g. Tests and assessments*

Multiple tests and assessments can be a challenge for any clinical trial participant, and autistic participants and their supporters are no exception. It is important that tests are explained and justified and that participants are supported throughout them to improve the experience and reduce dropouts.

General considerations

Take every opportunity to reduce the number and frequency of assessments.

- Remove the 'nice-to-have's'.

Clearly justify every required test or assessment so the participants and their supporters understand the importance of them.

- Explain why you need to conduct ECGs as they may raise concerns of heart-related side effects.
- Some participants and supporters may consider eye tracking to be burdensome or unimportant, so clearly explain this.
- Some participants and supporters will be sensitive to a suicidality measure unless explained early on.

Specific consideration
Blood draws, MRIs, and EEGs can be particularly challenging for paediatric and / or profoundly autistic individuals, so only conduct them when absolutely needed, justify them early in the trial, and have procedures in place to support participants.

- Create an environment where the participant and supporter feel comfortable and safe.
- Sedation and local anaesthesia may be considered for some assessments depending on the participant.
- Consider using a vibration device that attaches to the arm as a distraction technique from pain.
- Effectiveness of distractions will vary from person to person, so prepare a range of solutions based on preferences.
- UC Davis Health has produced a number of resources that help supporters to prepare autistic children for such tests (see an example here and full list in the resources section below).

Questionnaires can be long and time-consuming, so if required, trial organisers should carefully consider when to use them.

- Avoid ambiguous questions.
- Provide a remote option so the questionnaire can be completed at home.

Specific consideration
Paediatric and profoundly autistic participants may struggle to articulate how they feel in questionnaires, so train assessors to be aware of this.

Where possible, tests should be conducted remotely to reduce the need to travel, either through electronic PROs (ePROs), smart monitoring technology, or at-home visits.

Specific consideration
Consider the burden of tests on paediatric participants and school commitments. Consider the burden of tests on adult participants and work and supporters in general.

Ensure that trial assessments have some flexibility around the lives of participants and their supporters.

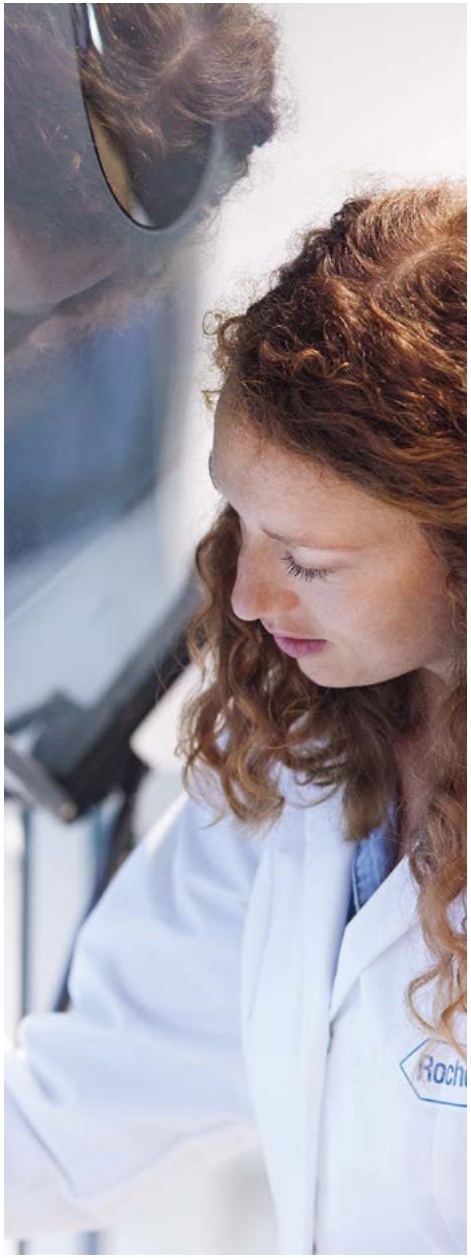
- I.e., provide several possible dates and times for appropriate assessments so that the participant and supporter can choose the most convenient occasion for them.

Allow time for participants and supporters to become accustomed to the site and visualise potential trial scenarios through visits and mock assessments before the study begins.

- If not possible, share pictures and / or clear descriptions of the trial site and equipment that will be used.
- Consider producing a 'walk through' video from the front door to the unit where the tests are conducted.

Consider conducting a questionnaire with participants or supporters on entry to gain their trial expectations.

- This can help to inform trial staff of any specific preferences and be used to compare expectations with actual experiences in a follow-up questionnaire (see Chapter 6: considerations after clinical trials).



h. Data sharing

Many trial participants and their supporters will want to retain control of their data and data sharing, particularly with the advancement of autism research into genetics. They may want to know how their data are used, and data conversations should be a key consideration in any trial.

General considerations

Provide a clear and upfront explanation of how participant and supporter data will be used, and consider giving different data sharing options.

Specific consideration
Explain what data can and cannot be retracted, and give the option to withdraw retractable data.

Data privacy will be a significant concern for some participants and supporters.

Ensure that any data (particularly genetic data) are stored and accessed securely and communicate this to participants and supporters.

Consider a tiered access model where data can be retrieved on a need-to-know basis.

Check before the study begins whether individual data can be shared, as this is often requested by participants and supporters but may not be possible.

Clarify in the ICF how data are used and who may have access to those data in the future.

Specific consideration
Supporters of autistic children and adult participants may wish to access their longitudinal data to understand how the intervention has impacted them.

Consider setting up trials so that it is easier to share trial data with recognised and approved initiatives for the advancement of autism healthcare.*

- Ensure that participants and supporters can opt in or out of this data sharing throughout and after the trial.

Ensure compliance with the relevant data protection regulations based on region i.e., REGULATION (EU) 2016/679.

**Consortium-based projects, such as The Autism Sharing Initiative (ASI)[31] and Simons Foundation Research Initiative (SFARI),[32] aim to build a secure network to share genomics and biomedical data gathered from research studies to improve the development of precision healthcare in autism. In addition, the Autism Innovative Medicine Studies-2-Trials (AIMS-2-Trials)[33] will explore how autism develops, from before birth to adulthood, how this varies in different people, and how biological markers indicate whether a person has or may develop particular characteristics.*

i. Site selection

Autistic people and their supporters value being in a comforting environment, and clinical trial sites should have this quality too. Consider if the study investigators are connected to the community as this might help with trust and recruitment.

General considerations

Consider locations that are closer to the community (i.e. close to major cities / transport links) and easier to access, rather than the most sophisticated or accredited sites.

Avoid using 'sterile' and windowless rooms as this can be off-putting and bring back bad memories of past experiences in doctors' offices.

- Provide comfortable seating.
- Use soft lighting and avoid flickering screens.
- Avoid background noise (even low-level noise can be disturbing).
- In some cases, you may want to make the setting personal and as true to 'real-life' as possible to help with adherence and compliance.

Specific consideration
A sensory environment may be attractive for some and off-putting for others, so consider offering different settings based on individual preferences.

Offer a selection of snacks, foods, and drinks that are available to both the participant and their supporter.

- This is particularly important if the trial runs for a long period during the day or covers mealtimes.
- Consider reaching out to the participant and their supporter with a choice of foods so they can pick before they arrive.
- Ask for any allergies.

Allow participants and supporters to share any individual needs and / or routines and accommodate these as best as possible before the trial begins.

Specific consideration
Consider that each participant and supporter will have individual limits when it comes to testing, so ensure these are known beforehand and respect them during the trial.

Provide entertainment on site.

Specific consideration
Paediatric and profoundly autistic participants will especially value toys, games, and smart tablets whilst they are waiting on-site.

Provide a room for participants and supporters to use if overly stressed and for general relaxation during the trial day.

General considerations

Importantly, provide a list in advance of what food and equipment will be available on site, so participants and supporters can plan what to bring / not to bring.

Allow participants to bring along toys and items of their choice to help them calm down in stressful situations.

Chapter 4:
Considerations when recruiting for clinical trials

Chapter summary

- Depending on the country, local rules and desired trial population, partner with umbrella and regional autism organisations, healthcare professionals, hospitals, speciality clinics, peer support groups, nurseries, and schools for recruitment.
- Ensure that recruitment materials cover the key aspects of the trial, balance participant and supporter expectations, and are accessible and inclusive.
- Where possible, host webinars in collaboration with autism advocacy groups, which cover the fundamentals of clinical trials and the science behind autism to provide general clinical trial awareness. Note: this depends on the country where the clinical trial is being run and what is being tested.

a. General clinical trial awareness

There is a general lack of awareness around clinical trials amongst the autism community, which is a barrier to participation. The community requires general trial information to build interest and enthusiasm.

General considerations

Consider hosting webinars, partnered with autism community organisations, which cover the basics of a clinical trial – what they are, how they are conducted, and why they are important for the autism community.

- These should include understandable summaries of recent developments in autism research and the method of action for different interventions.

Reach out to umbrella organisations (organisations that group together national or regional patient organisations representing autism, such as Autism Europe) and those at a local and regional level, such as Autismo Burgos, to disseminate clinical trial material (as appropriate per local compliance regulations).

Aim to have your trial documented in the 'Participate in Research' section on relevant patient organisations' websites to improve awareness of the trial.

b. Specific clinical trial awareness and recruitment

While some members of the autism community know of clinical trials and have expressed an interest in participating in them, they do not necessarily know who to speak with to join a trial.

Specific considerations

Reach out to HCPs (specifically autism developmental specialists and those working in university-based clinics) within your network, as they may already know potentially suitable participants.

Recruit potential participants and supporters through neurological and behavioural therapy departments in hospitals and speciality clinics.

Raise awareness through schools, clinics, and primary care centres to reach autistic children and their supporters who may not be associated with autism community organisations (as per local regulations and in regions where culturally appropriate).

Consider contacting peer support groups to raise awareness of clinical trials.

Recruit participants from a variety of cultural, socioeconomic, and ethnic backgrounds to represent the autism community more accurately.

c. Information needs and material development

During the recruitment stage, participants and supporters will have specific information needs. It is unlikely that they will trust the trial or participate if you do not meet their needs.

General considerations

Key information for participants and supporters at this stage are:

- who can participate (to set expectations)
- the aims of the trial
- the trial drug, its action, safety and effectiveness
- expected time and travel commitments
- expected tests and measurements.

Ensure that trial information balances the expectations of participants and supporters for full transparency.

- E.g., the trial may or may not provide personal benefits, but contributions to research will be valuable to the wider autism community and may bring personal benefits in the future.

Materials should be succinct and readable for a lay audience (follow plain language guidelines).[34]

Provide the information in a variety of formats (print, visual, audio, and video) to increase accessibility.

Specific consideration
Ensure materials are age appropriate (child vs. adult participants).

Disseminate information through autism community organisations, waiting room clinics, hospitals, and social media (will depend upon local compliance regulations).

Materials should be relatable to the participants and their supporters.

Specific consideration
Use images of people that look like the expected participants and their supporters i.e., similar age, diverse ethnicities, etc.

Communicate that all information collected from participants and supporters will be confidential.

Ensure that all materials are ethically approved and compliant in the respective region.

Chapter 5:
Considerations when conducting clinical trials

Chapter summary

- Logistical issues will be the major barrier for many participants and supporters, so offer food, entertainment, transport support, clinical trial 'buddies', and overnight accommodation (if necessary).
- Build trust from the beginning by listening to concerns, appropriately training staff, being punctual, and following agendas.
- Participants and supporters must feel motivated to continue in the trial through clear communication.
- Ensure that participants and supporters know how to receive side effect support and the support is accessible.
- Work alongside supporters to aid treatment adherence and clearly explain the required dosing schedule and communicate any off-site assessments that will be required.

a. Logistics

Most concerns from participants and supporters stem from logistical issues, so tackling these will reduce dropouts.

General considerations

Offer free transportation to and from the trial site, with door-to-door transport available if needed.

Offer child-care assistance for participants or supporters.

Before participants arrive at the site for the first time, provide a description of how the site looks, how to get to the clinic, where to park, and how to get to the entrance from the parking facilities to reduce anxiety.

- Using photos and / or videos to help describe the site can be helpful (as long as the rooms and site do not change).
- Provide the name and picture of the first site contact so participants and supporters know who to meet.

Provide free and reserved parking for participants and supporters throughout the trial.

Provide participants and supporters with a floor plan so they know exactly how to find facilities in the clinic.

Minimise the amount of time participants and supporters are on site by collecting as many outcomes as possible in the same period.

Offer clinical trial 'buddies'; partnering participants and supporters within the same trial so they can support one another throughout.

b. Build trust

Building trust between trial staff and participants and supporters from the beginning is vital to a positive trial experience and reducing dropouts.

General considerations

Train staff to listen to the concerns of participants and supporters and answer questions fully and clearly.

- Provide participants and supporters with a list of frequently asked questions that can help them to communicate with trial staff about key parts of the trial, i.e. why will I need to have a blood test 1-week after the trial starts?

Specific consideration
Train staff depending on the age, level of support needs, IQ, and communication ability of the participants.

Train staff to consider the needs of each individual participant and the best ways to make them feel comfortable. E.g., some participants may be light-sensitive, so dimming the lights to a suitable setting and avoiding blinking lights may make them feel more comfortable.

Always follow schedules that have been previously shared with participants and supporters.

- Aim to have no waiting times or queues.
- Start activities and assessments on time.
- If changes to schedules absolutely need to be made, justify these, and apologise promptly and explain why.

Ensure there is continuity of staff.

- Assign specific trial staff (nurses, clinicians etc.) to groups of participants and supporters where possible so they see the same faces throughout the trial.

Specific consideration
Consider having pictures, names, and background information of the staff in the waiting area so participants know who works there. Also offer this as a leaflet so the participants and supporters can take this home and prepare for their next visit.

c. Communication during the trial

Participants and supporters should feel comfortable and well informed through regular communication from the trial team. The trial team should also prepare a communication for employers, schools, other HCPs, and therapists, so that the participant or supporter can inform the necessary stakeholders of their involvement in the study.

General considerations

Ensure that language is simple and terminology is defined and easy to understand.

Specific consideration
Provide plain language summaries that are readable by children or individuals with mild to moderate cognitive impairments.

Translate all materials appropriately for your setting, including into local languages.

Participants and supporters will be encouraged with study updates, such as newsletters, after assessments, and at certain time points.

- Feedback should include results if possible or a thank you to acknowledge the time and effort put in by participants and supporters.

Any communication should be motivating and inspiring.

Do not overburden participants and supporters with too frequent and unnecessary information.

Specific consideration
Allow participants and supporters to access information whenever they need it as needs will differ between individuals. This may be in the form of handouts, brochures, or a trial website.

Still provide the supplementary information in a separate place for those who may wish to access it.

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d. Supporting side effects

Side effects will be a key concern for many participants and their supporters, and procedures to support them must be known and available.

General considerations

Assess side effects frequently and use the correct, standardised methods.

Make participants and supporters aware of how to report any side effects at the beginning of the trial.

Offer an easily accessible 24/7 helpline for side effect advice and support whilst participants are away from the trial site.

Specific consideration
Provide a non-verbal option to receive side effect support (email or text).

If available, share details on types and frequency of side effects from earlier trials ahead of administering the trial drug.

Provide materials (in various formats) that discuss how to best deal with manageable side effects at home.

- Materials should discuss how side effects will impact normal activities, such as working, physical activity, or driving.

Specific consideration
For paediatric participants and those with low communication and cognitive skills, explain how supporters can recognise side effects.

If suicidality is a known or suspected side effect, ensure that a safety plan is put in place before randomisation onto the trial drug or control (even if the participant is not already at risk of suicide).

Offer psychological and mental health support for both participants and supporters throughout the trial.

e. Supporting treatment adherence

Difficulties with adherence to treatment and digital tools will be highly diverse across autistic individuals, but certain actions can be taken to ensure procedures are in place to support adherence. This may include the use of frequent reminders or apps to help with adherence.

General considerations

Depending on pharmacokinetics, the preferred dosing schedule would be once a day.

Where possible, reduce the number of required daily doses (e.g., opting for twice daily dosing over three-times daily) to improve treatment adherence.

Pill box organisers can be easily distributed and aid adherence.

Specific consideration
For adult participants, consider how you can make the study medication more portable so they can be easily transported and used during a work day.

(This is less of an issue for paediatric participants as a school nurse typically helps with administration.)

Some autistic people and supporters already use formal day plans. Consider how a treatment adherence plan can be integrated into day plans.

Identify individual adherence challenges in discussions with the participant and / or supporter so appropriate support can be put in place.

Ensure that treatment adherence is carefully monitored by trial site staff with assistance from the supporter.

Consider using telemedicine and video apps to encourage and monitor adherence.

Provide a good explanation of the required dosing schedule to participants and supporters.

Adherence to digital tools (as the investigated treatment or as part of a drug-based trial) must not be underestimated and should be supported.

Chapter 6:
Considerations after clinical trials

Chapter summary

- Clearly discuss whether there is an after-care package, what is included, length of after-care, how to access it, and who will receive it.
- Ensure participants and supporters are followed-up in due course with a lay summary of the trial data and are kept informed of the treatment's progress through research and beyond.
- Offer an open-label extension where appropriate and clearly explain what this means for participants and supporters.
- Collect clinical trial experience feedback so that study teams can learn what works well, what does not, and continuously improve.

a. After-care information

Participants and supporters value a structured support plan post-trial, and this will likely be a key part of their decision to participate.

General considerations

Provide clear and explicit information on whether there is an after-care package, what is included, what are the trial sponsors' responsibilities in the package, and how long after-care will be provided.

- After-care should include support for any side effects and psychological / mental health support (particularly for those who had negative or neutral outcomes for the trial or received a placebo).
- Between 5 – 10-years is generally considered a suitable amount of time for after-care.
- Need to consider and clearly explain upfront what after-care is offered to those who dropout before trial completion.

A helpline should be available to participants and supporters post-trial if they have any questions or worries about side-effects.

Specific consideration
Provide a non-verbal contact alternative, such as a chat system or phone number for text messaging.

Try to assign participants and supporters to the same trial staff members to ensure continuity of after-care.

Offer holistic after-care support and links to other associations that can help.

Specific consideration

- If child participants have taken time out of school during the trial, offer educational support (or signpost external resources).
- If adult participants need a new job or can attain a new one, offer career support (or signpost external resources).

Collect feedback from participants and supporters on their clinical trial experience to compare with expectations and help improve future trials.[35]

b. Follow-up with study results

Participants and supporters have given up considerable time and effort to the trial and deserve to be informed of the study results in good time.

General considerations

Include both positive and negative trial results.

Specifically explain negative results with the important detail that they are still beneficial for autism research.

Clearly summarise what the results mean for the autism community.

- Present the information in easily understandable lay language.

Specific consideration
Provide summary results in a format that is appropriate for the participants (i.e., video for paediatric or profoundly autistic participants).

Include a sincere thank you to the participant and their supporter.

Provide a long-term follow-up that includes details on later trial phases and whether the treatment succeeded and made it to market.

c. Open-label extension

Having an open-label extension built into the trial (Phase 2 and above) will be appealing to participants and supporters.

General considerations

Clearly explain what an open-label extension means for the participants and their supporters.

- I.e., all participants, regardless of whether they received the active drug / device / psychotherapy or placebo, are invited to continue the trial for a further period to gain more data on how the drug works and how safe it is.

In cases where the study does not continue despite individual participants having favourable results, trial staff need to explain that this does sometimes happen and offer support.

Chapter 7:
Future steps and prioritised recommendations

The purpose of this guidebook is to ensure that future autism clinical trials are truly accessible to autistic people and their supporters. Trial organisers should also consider many of these recommendations for any clinical trials to make them more friendly for any potential autistic participants.

Not every recommendation in this Guidebook will be possible for all clinical trials. However, there are some vital steps that trial organisers should take, which The Clinical Trials in Autism Council have identified.

Key consideration before designing clinical trials

The ability to personalise the clinical trial experience to the extent possible and rapidly adapt to any feedback will be key success factors for any autism clinical trial.

Prioritised considerations

Designing clinical trials

1. Include members of the autism community (representing subgroups relevant to the clinical trial population) in the study design process.
2. Take every opportunity to reduce the number and frequency of assessments.
3. Choose endpoints that will be important based on participant age during the trial and for future life, such as those found in the World Health Organization Quality of Life Abbreviated Scale (WHOQOL-BREF), and those that reflect factors like self-sufficiency (living independently relevant to the individual's situation, socialising, autonomy etc.), employability, and self-injury.

Recruiting for clinical trials

1. Provide key information for participants and supporters at this stage, including:
   - who can participate (to set expectations)
   - the aims of the trial
   - the trial drug, its action, safety, and effectiveness
   - expected time and travel commitments
   - expected tests and measurements.
2. Recruit participants from a variety of cultural, socioeconomic, and ethnic backgrounds to represent the autism community more accurately.
3. Provide the information in a variety of formats (print, visual, audio, and video) to increase accessibility.

Conducting clinical trials

1. Most concerns from participants and supporters stem from logistical issues, so tackling these will reduce dropouts (see Chapter 5a).
2. Offer an easily accessible 24/7 helpline for side effect advice and support while away from the trial site.
3. Building trust between trial staff and participants and supporters from the beginning is vital to a positive trial experience and reducing dropouts (see Chapter 5b).

After clinical trials

1. Provide clear and explicit information on the after-care package, what the responsibilities of the trial sponsor in the after-care package are and how long it will be provided.
2. Offer an open-label extension when possible.
3. Clearly summarise what the results mean for the autism community.

Roche funded the production of this Guidebook, and it was developed in collaboration with the autism community through representatives of The Clinical Trials in Autism Council.

Resources

For general materials on clinical trials, please refer to the European Patient Academy on Therapeutic Innovation (EUPATI) website.

The following trial specific resources may be beneficial when designing and conducting clinical trials. Many of these materials can be reused and adapted, but please refer to the original source material for copyright information.

General language resources and community engagement and co-creation

Easy-to-read information guidance from Inclusion Europe

Plain language summaries (PLS) of peer-reviewed publications and conference presentations: practical 'How-To' Guide for multi-stakeholder co-creation

How-to guide for patient engagement in the early discovery and preclinical phases

How-to guide on patient engagement in clinical trial protocol design

Study participant feedback questionnaire toolkit

Autistic children and adolescent resources:

Assent:

Assent Form #2". Social Development Research Group, The University of Manchester

Child Assent Form aged 4-8 years". IAMHealth, King's College London.

Consent:

Verbal Information and Consent Form." DART, The University of Edinburgh.

Interview Consent Form." Centre for Research in Autism and Education (CRAE), University College London (UCL) and Ambitious about Autism.

Tests and assessments:

Getting my blood drawn at the UC Davis Mind Institute

Welcome to the MIND Institute and the STAAR Study! UC Davis Mind Institute

Welcome to the Imaging Research Center, UC Davis Mind Institute

Social Story: Autism Phenome Project, UC Davis Mind Institute

Information Sheet #1". Social Development Research Group, The University of Manchester.

Information Sheet #2". Social Development Research Group, The University of Manchester.

Information Sheet for High Ability/ Verbal Group aged 11-15 years". IAMHealth, King's College London.

Information Sheet for Medium Ability Group aged 11-15 years". IAMHealth, King's College London.

Information Sheet for Minimally Verbal Group aged 4-8 years". IAMHealth, King's College London.

Information Sheet for Minimally Verbal Group aged 11-15 years". IAMHealth, King's College London.

Visual Timetable/ Plan of Assessment Day aged 11-15 years". IAMHealth, King's College London.

Autistic adult resources:

Consent:

Consent Form." DART, The University of Edinburgh

Tests and assessments:

"Brain Imaging Information Pack." WARC, The University of Cardiff

Participant Information Sheet – MRI study." DART, The University of Edinburgh.

Focus groups:

Information Pack for Focus Group." Social Development Research Group, The University of Manchester.

Information Pack for Focus Group." Centre for Research in Autism and Education, UCL.

Arriving at the trial site:

Information Pack." DART, The University of Edinburgh.

Feedback:

Study Participant Feedback Questionnaire (SPFQ)

Supporter resources:

Tests and assessments:

ERP Handout for Parents

MRI Handout for Parents

Phlebotomy (Blood Draw) for Parents

IEEPO Personalised Healthcare Hub

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