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Extended Research Article

A group intervention for parents and carers to recognise and understand restricted and repetitive behaviour in autistic children: a multisite RCT

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Abstract

Background: Restricted and repetitive behaviours vary greatly between autistic people. Some are a source of pleasure or create opportunities for learning; however, others are functionally impactful and may cause harm. We have developed a parent/carer group intervention (Understanding Repetitive Behaviours), for families of young autistic children, to help parents/carers to recognise, understand and respond to their child's functionally impactful restricted and repetitive behaviours.

Objectives: To evaluate the clinical and cost-effectiveness of the Understanding Repetitive Behaviours intervention.

Design: A clinical and cost-effectiveness, multisite randomised controlled trial of the Understanding Repetitive Behaviours intervention versus a psychoeducation parent/carer group Learning About Autism (*n* = 250; 125 intervention/125 psychoeducation; ~ 83/site). Analyses completed using intention-to-treat principles.

Setting: Three NHS trusts and universities across England and Scotland.

Participants: Parents/carers aged 18 and over, with an autistic child between 3 and 9 years and 11 months, sufficient spoken and written English, willing to be randomised and attend all group sessions, who agree to maintain their child's current medication up to 24 weeks and not to participate in any other trials up to 24 weeks.

Intervention: An 8-week parent/carer intervention that was delivered face to face and online using a secure digital platform. Randomisation was at the child level using equal allocation ratio.

Information: Research associates and research leads were blind to trial arm allocation.

Main outcome measures: The primary outcome is the Clinical Global Impression – Improvement scale, based on child data. Economic outcomes included incremental cost per additional child achieving at least the target improvement in Clinical Global Impression – Improvement scale, cost consequences and incremental cost per quality-adjusted life-year gained were calculated for the comparison of the Understanding Repetitive Behaviours and Learning About Autism groups.

Results: Two hundred and sixty-two participants were consented and 227 randomised to either the Learning About Autism (113 participants) or the Understanding Repetitive Behaviours (114 participants) arms of the trial. Seventy-two families did not provide data at primary end point. Data were available for 81 Learning About Autism and 74 Understanding Repetitive Behaviours families at 24 weeks. No differences were found between the arms on the Clinical Global Impression - Improvement scale. Analysis of the secondary outcomes indicated that children in the Understanding Repetitive Behaviours arm were more likely to be rated responders in target restricted and repetitive behaviours at 24 weeks. Improvement in parent and family functioning was apparent across both arms over time, with no evidence of differences between the arms.

Five serious adverse events were reported, none of which were related to study participation.

Conclusions: The study had a less than expected follow-up at the primary end point and was therefore underpowered. Findings related to the potential clinical effectiveness of Understanding Repetitive Behaviours remain inconclusive. Understanding Repetitive Behaviours is unlikely to be considered cost-effective at 12 months. Future work should determine what the mechanisms of change in functionally impactful restricted and repetitive behaviours are and consider longer time horizons and different methods of valuing benefits for autistic children.

Trial registration: This trial is registered as ISRCTN15550611.

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List of abbreviations

ABC	adaptive behaviour composite
ADOS-2	Autism Diagnostic Observation vSchedule-2
AFEQ	Autism Family Experience Questionnaire
APSI	Autism Parenting Stress Index
ASD	autism spectrum disorder
BNF	British National Formulary
CEA	cost-effectiveness analysis
CHU-9D	Child Health Unity 9D
CI	confidence interval
CNTW	Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust
CRN	Clinical Research Network
CUA	cost–utility analysis
DMC	Data Monitoring Committee
eCRF	electronic case report form
EoI	expression of interest
ESI	events of special interest
GBP	Great British pounds
CGI-I	Clinical Global Impression – Improvement scale
GCP	good clinical practice
GEE	generalised estimating equation
HTA	Health Technology Assessment
ITT	intention to treat
LAA	Learning About Autism
NAS	National Autistic Society
NCTU	Newcastle Clinical Trials Unit
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
ONS	Office for National Statistics
OR	odds ratio
PACT	Paediatric Autism Communication Trial
PI	principal investigator
PIC	Participant Identification Centre
PPI	patient and public involvement
PSE	parent/carer self-efficacy
QALY	quality-adjusted life-year
RA	research associate
RBQ-2	Repetitive Behaviour Questionnaire – 2
RCT	randomised controlled trial
RfPB	Research for Patient Benefit
RRB	restricted and repetitive behaviour
RUPP	The Research Units on Paediatric Psychopharmacology and Psychosocial Intervention Programmes
SAE	serious adverse event
SD	standard deviation
SRS-2	Social Responsiveness Scale – Second Edition
STM	senior trial manager
SUR	seemingly unrelated regression
SUQ	Service User Questionnaire
TBV	target behaviour vignette
TEWV	Tees, Esk and Wear Valleys NHS Trust
TM	trial manager
TMG	Trial Management Group
TSC	Trial Steering Committee
TTQ	time and travel questionnaire
URB	Understanding Repetitive Behaviours
VABS-3	Vineland Adaptive Behaviour Scales 3
WEMWBS	Warwick–Edinburgh Mental Well-being Scale
WGEE	weighted generalised estimating equations

Plain language summary

Autistic children often do the same behaviours repeatedly, have specific interests or like things to stay the same each time something happens. Often this does not cause difficulties and these behaviours and interests can be helpful and fun. However, sometimes they may cause harm to the child, put them at risk and/or restrict opportunities for learning or impact on their family life. Working with parents/carers of autistic children, we developed a parent/carer programme (Understanding Repetitive Behaviours) to help parents/carers to recognise and understand these behaviours and learn approaches to reduce their child's use of behaviours that have a functional impact. This study aimed to find out whether our parent programme was helpful and good value for money.

The 227 families who agreed to participate in the study were allocated by chance into two separate groups, either the Understanding Repetitive Behaviours group or another parent/carer group (Learning About Autism). Parents/carers provided us with lots of information about their child and themselves at the beginning of the study, and then again after 10, 24 and 52 weeks. This study took place during the COVID-19 pandemic, and we had to make changes to both the delivery of parent programmes and how the research took place to comply with government guidelines. Unfortunately, 72 families did not complete the follow-up at 24 weeks. This meant that we were unable to find out whether or not the Understanding Repetitive Behaviours intervention was effective. We therefore cannot recommend either parent group intervention to help parents know how best to respond to their autistic child's impactful repetitive behaviours. Despite this, we were able to show that both Understanding Repetitive Behaviours and Learning About Autism can be delivered by trained NHS professionals and that both groups are safe for families. Also, some families who attended Understanding Repetitive Behaviours reported improvement in their child's functionally impactful repetitive behaviours at 24 weeks and parents/carers in both groups reported more confidence, greater well-being and less stress up to 1 year afterwards, indicating that both parent groups were beneficial and supportive for parents of autistic children.

Scientific summary

Background

Restricted, repetitive and stereotyped patterns of interests, behaviours and activities [restricted repetitive behaviour (RRB)] such as repetitive movements, rigid routines, unusual preoccupations, circumscribed interests, resistance to change and sensory sensitivities form one of two key symptom domains required for a diagnosis of autism spectrum disorder (ASD). Frequently, RRBs are reported by autistic people to be enjoyable, functional and helpful. RRBs can be a source of great pleasure. They may provide a basis for friendship and can also build areas of strength, supporting skill development and yielding employment opportunities. For these reasons, and in line with the non-normalising agenda of neurodiversity, the default pathologisation of RRB should be resisted.

However, autistic people also report that restricted and repetitive behaviour (RRB) may also be an outward sign of anxiety or distress, and some behaviours can have a functional impact, causing harm to the child or restricting their access to learning or participation in their community. In addition, families can find understanding this repertoire of behaviours particularly difficult, both to understand and in terms of their family impact. Furthermore, RRB can interfere with family functioning and can cultivate negative parenting styles, which in turn may be detrimental to the autistic child's development. Currently there are no evidence-based interventions available that focus specifically on supporting parents/carers to understand and respond to their child's functionally impactful RRB.

The Understanding Repetitive Behaviour intervention (URB) was developed in collaboration with parents/carers. Understanding Repetitive Behaviours (URB) is an eight-session, parent-mediated group intervention that aims to increase parents/carers' understanding of their child's RRB and support them to develop strategies to differentiate between RRB that are beneficial or pleasurable for their child and those that have potential to cause harm (hereby known as functionally impactful RRB), and reduce engagement in these repetitive behaviours.

Objectives

1. Compare the clinical effectiveness of the URB intervention for NHS community clinical practice with psychoeducation, for the management of functionally impactful RRB in autistic children at 24 and 52 weeks follow-up.
2. Assess the cost-effectiveness and cost consequences of the URB intervention compared with an autism parent/carer psychoeducation group (Learning About Autism; LAA) at 52 weeks follow-up.

Methods

The study was a clinical and cost-effectiveness, large-scale, multisite randomised controlled trial (RCT) of the URB parent group intervention versus the LAA psychoeducation parent group (current best practice) for parents of autistic children aged 3 years to 9 years 11 months. All analyses were done under an intention-to-treat principle. The primary outcome was at 24 weeks. The economic evaluation was conducted from the perspective of both NHS costs and family access to local community services.

Parents and carers aged 18 years and older were eligible for study entry if their child met the following criteria:

1. Aged 3 to 9 years 11 months at the time of consent with a clinical diagnosis of autism spectrum disorder (ASD), across a range of functioning levels and abilities (verbal and nonverbal).
2. Parents/carers with sufficient spoken and written English to provide written informed consent and complete the assessments, including being able to identify one or more functionally impactful RRB and participate in the group-based programme.

3. Parents/carers were willing to be randomised and attend all the group sessions for the allocated arm of the study and agree to maintain their child's current medication regime up to 24 weeks (unless change is advised by the child's clinician) and agree not to participate in any other trials while involved in the trial up to 24 weeks.

Parents/carers were not eligible for study entry if their child met any of the following criteria:

1. no clinical diagnosis of autism or ASD;
2. no functionally impactful RRB could be identified;
3. currently taking part in another parent group-based programme trial;
4. had a sibling already taking part in this study;
5. parents/carers had a severe learning disability or a significant mental health disorder that would interfere with their ability to take part in a group-based programme.

Randomisation

Randomisation was at child level using an equal allocation ratio. Each parent/carer was automatically considered in their child's randomisation group. Due to the nature of the study and the few factors (age, gender and ethnicity) that needed to be accounted for in the randomisation, a minimisation scheme instead of stratified randomisation was used to minimise sample fragmentation due to the number of strata and to avoid accidental imbalance between the URB group and the LAA comparison group across the levels of age, gender and ethnicity.

Study setting

The URB and the LAA parent/carer groups were delivered in community settings in different geographical locations across the three sites in North East England and Scotland. The first participant was randomised on 13 November 2018. The final participant was randomised on 15 September 2020. Due to restrictions resulting from COVID-19, all baseline and follow-up visits were conducted via telephone after March 2020 and delivery of both interventions moved from face-to-face delivery to online platforms. A minority of families (n = 47) completed their participation in the trial, up to the 24-week follow-up assessment, prior to the onset of COVID-19 restrictions, and therefore only 25% of families recruited to the study experienced the trial in its original format.

The intervention

Understanding Repetitive Behaviours is designed to help parents/carers of young autistic children to recognise, understand and learn how to manage their child's functionally impactful RRB. It is an eight-week manualised intervention designed to be delivered by trained community-based professionals with knowledge and experience of working with young autistic children and their families. Each weekly session lasts for approximately two hours. Each parent/carer is provided with a manual, related weekly materials, and individual support to identify strategies to address functionally impactful RRBs. 'At home' activities are set each week for parents/carers and children to complete between sessions.

Learning About Autism is an 8-week manualised parent/carer psychoeducation group that acted as an attentional control. It is designed for parents/carers of young autistic children and focuses on understanding what is autism. It is designed to be run in the community with trained professionals who have experience of working with young autistic children and their families. Each weekly session lasts for approximately 2 hours. The groups offer parents and carers psychoeducation to develop understanding of autism and what that means for their child. LAA did not include any specific information about the role and functions of RRB, or tailored strategies to manage functionally impactful RRB.

Primary clinical outcome measure

Clinical Global Impression – Improvement scale (CGI-I) provides a standardised framework to assess how much behaviour has improved or worsened relative to the child's baseline state using a seven-point scale. A trained researcher, blind to group allocation, rated global improvement in how much the child's functionally impactful RRB had changed over the 24 weeks (from baseline to primary end point). The data included available child outcome measures from baseline and week 24 [Social Responsiveness Scale – Second Edition (SRS-2) (baseline only), parent/carer and teacher Repetitive Behaviour Questionnaire – 2 (RBQ-2), Adaptive Functioning (Vineland Adaptive Behaviour Scales 3 (VABS-3), target behaviour vignettes (TBVs)] to make the rating about change for each child.

Economic evaluation: To assess the costs and benefits of the URB intervention a cost-effectiveness analysis (CEA), cost–utility analysis (CUA) and cost-consequence analysis (CCA) were carried out. For the CEA the primary outcome is the cost per incremental improvement of CGI-I scale. For the CUA, QALYs were used as the primary outcome, both for the parent/carer's quality of life (using the EQ-5D-5L) and for the child's quality of life [using the Child Health Unity 9D (CHU-9D)]. The secondary outcomes were expressed using a balance sheet approach for the CCA, summarising the costs and which of the secondary outcome measures favour LAA and which favour URB.

Secondary clinical outcomes measures: Secondary outcome measures at the level of the child included parent/carer and teacher reports of the child's RRB (RBQ-2 and Teachers RBQ), RRB TBVs and VABS-3. Secondary outcome measures at the level of the parent/carer and family included measures of parent/carer self-efficacy (PSE), parent/carer stress [Autism Parenting Stress Index (APSI)], parent/carer well-being [Warwick–Edinburgh Mental Well-being Scale (WEMWBS)] and family functioning [Autism Family Experience Questionnaire (AFEQ)].

Results

Fidelity analysis indicated that both URB and LAA were delivered with fidelity to the manual. Five SAEs were reported during the duration of the study, none of which were deemed to be associated with participation.

Thirty-one per cent of data were missing at the primary end point. According to the initial sample size calculation for this study, to detect a 20% improvement rate between the URB intervention and LAA group at 24 weeks (proportion of events in the URB 25% and LAA 5%), assuming 10% intra-parent/carer group correlation and equal allocation ratio a minimum of 179 families were estimated to be needed to achieve 80% power (N = 224, 90% power). A post hoc power calculation based on the data available at the primary end point (N = 155) and the same parameters used in the initial sample size calculation indicated 70–75% of the power is retainable. This means that with the available data at 24 weeks, the trial collected less than expected follow-up data and so is unable to answer, with any certainty, whether or not the URB intervention is effective compared to the LAA group.

No evidence of a difference was found between the URB and LAA arms for the primary outcome measure (CGI-I) at 24 weeks.

Analysis of the secondary outcomes indicates improvement in targeted functionally impactful RRB identified by parents/carers at baseline at 10 and 24, but not 52 weeks and reduction in impact on the family unit for those families who were randomised to the URB arm, but not those who attended the LAA. Improvement in parental functioning (self-efficacy, stress and well-being) and family functioning were apparent across both intervention programmes, with no evidence of differences between the two approaches.

Regarding the results of the economic evaluations for the CEA, the incremental cost per additional child achieving the target difference in CGI-I was £36,700 for URB compared with LAA. For the CUA using the imputed data set (n = 199), the incremental cost per QALY for URB compared with LAA is £44,500. At a threshold of £20,000 per QALY there is a 37% chance of URB being considered cost-effective compared to a 63% chance of LAA being considered cost-effective. For the child's QALYs using the CHU-9D, LAA was both less costly and slightly more effective.

Conclusion

Strengths and limitations

This is the first large-scale RCT to investigate the clinical and cost-effectiveness of an early intervention for autistic children focusing on functionally impactful RRB – a research priority highlighted by parents of young autistic children. The RCT also used an attentional control, a new development in the evaluation of early interventions in autism. The primary outcome provided a standardised framework of overall functioning rather than simply assessing changes in the specific behaviours targeted using the intervention. Both interventions were delivered by practitioners based in the community rather than in specialist centres and the fidelity of delivery of both interventions was high even taking into account the changes necessitated by the COVID-19 pandemic.

Unfortunately, probably at least in part due to the COVID-19 pandemic, the relatively high attrition rate at 24 weeks meant that the study collected less than expected data at the primary end point. We are also aware that there are other potential factors that may have contributed to our lack of difference between the URB and LAA parent groups.

Areas for further research

Future research should focus on trying to determine what the mechanisms of change in functionally impactful RRB are for autistic children. Future research could potentially focus on a longer longitudinal follow-up, which could be utilised in economic modelling studies over a longer time horizon. In addition, different approaches to measuring benefit for parent/carer interventions for autistic children could be utilised to capture both potential positive change and adverse outcomes that are relevant to families of autistic children and meet the priorities of the autism community. These should include relevant non-health effects. From a methodological point of view, it will be important to determine how recruitment and retention of families can be improved and specifically how participation of autistic people from non-white backgrounds can be improved.

Trial registration

This trial is registered as ISRCTN15550611.

Funding

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Chapter 1 Introduction

Terminology used in the report

In this report (and our published trial protocol[2]) we use identity-first language to describe autistic people, in line not only with the preferences of many English-speaking autistic people, but also argued by many to be less stigmatising than the alternative, person-first language.[3,4] In addition, we use a novel term 'functionally impactful RRB' to describe a subset of behaviours under the umbrella of the Restricted, Repetitive and Stereotyped Patterns of Interests, Behaviours and Activities [restricted and repetitive behaviours (RRBs)] diagnostic domain which was targeted in the intervention being evaluated. This comes from a desire to refer to a group of RRB that have detrimental consequences for the child themselves, where those consequences are defined as far as we can with inclusion and autistic flourishing in mind. Previous reports from our team (e.g. the trial protocol[2]) used the term 'challenging RRB' for the same purpose, but we have changed this to reflect concerns that this terminology centres the parent/carer/practitioner perspective (the person facing the challenge) more than the child perspective.[4] A shift to the concept of functional impact focuses more precisely on why these RRB can be considered valid intervention targets.

Restricted and repetitive behaviours such as repetitive movements, rigid routines, unusual preoccupations, circumscribed interests, resistance to change and sensory sensitivities form one of two key symptom domains required for a diagnosis of autism spectrum disorder (ASD), hereafter referred to as autism.[5] While not exclusive to autism and occurring in typical development, as well as in children with learning disabilities, research consistently indicates increased frequency, duration, range and intensity of RRB in autistic children.[6] Frequently, RRBs are reported by autistic adults to be enjoyable, functional and helpful. RRBs can be a source of great pleasure, both in the physical domain (i.e. the positive experience of repetitive movement or 'stimming') and as an expression of passionate interest (e.g. collections, hobbies). They may provide a basis for friendship, for example, when meeting people with a shared interest, or within a fandom. They can also build areas of strength, supporting skill development and yielding employment opportunities.[7,8] For these reasons, and in line with the non-normalising agenda of neurodiversity, the default pathologisation of RRBs should be resisted.

However, RRB may also be an outward sign of anxiety or distress, deserving of attention and care from others.[9] We know that families can find understanding this repertoire of behaviours particularly difficult, with parents spontaneously identifying RRB as the most difficult aspect of parenting their autistic child.[10] High rates of RRB can also be stigmatising[11] and lead to agitation or aggression, if interrupted[12] RRB can interfere with family functioning, and can provoke negative parenting styles.[8,12] In the last 5–10 years, there is emerging evidence for the immediate and longer-term benefit of interventions to support parents' early interactions with their young autistic child, for example, promoting their responses to their autistic child's social and communication development – the other key behavioural domain required for a diagnosis.[13] However, at the time this study started, there are no evidence-based interventions available that focus on supporting parents to understand and respond to their child's RRB. 'At home' activities are set each week for parents/carers and children to complete between sessions.

Restricted and repetitive behaviours are a core symptom domain for a diagnosis of ASD and thus RRBs are present in all autistic individuals. RRB can take a variety of forms and vary in the kind and degree of impact. Narrowness of focus, inflexibility, perseveration of interest in activities and insistence on sameness reflect the restricted aspect of this domain, while repetition is demonstrated in repetitive speech, routines, rituals and rhythmic stereotypies.[14] For parents, RRB can be extremely difficult to understand and as a result it can be difficult to know how to support their child. For example, a family may avoid taking their 9-year-old to the shops if every time they go into the supermarket

the child responds to the sensory experiences of the lights and the presence of other people with disruptive spinning and screaming. The reduction in autonomy consequent on this kind of daily limitation can negatively impact the child directly, via a reduction of their opportunities to experience the world, and indirectly via parent stress and parenting choices.

We have on reflection, and taking into account feedback from clinicians who delivered the programme and members of our dissemination advisory group, changed the name of our programme to Understanding Repetitive Behaviours (URB). This better reflects the neurodiversity affirming approach of the programme and the research and clinical team.

Developmental origins of restricted and repetitive behaviour

Restricted and repetitive behaviours are not exclusive to autism; they are also seen within typical and delayed development. A range of adaptive functions of RRB are widely recognised.[15] Indeed, Thelen[16] identified that stereotyped behaviours in the early years contribute to neuromuscular development and the acquisition of skilled motor actions. Repeating certain actions with toys and uttering the same sounds or words over and over again are considered vital for developmental progress.[16] For example, seemingly obsessional interests such as dinosaurs can help children develop attention to detail and language skills. In typically developing children, we often see a reduction in RRB at around 3–4 years of age.[17] However, although these early behaviours are similar for autistic children, the frequency and types of RRB they display vary according to age and cognitive ability and do not necessarily decline over time as children mature.

A lack of typical decline in frequency of RRB as autistic children grow up is not, in and of itself, a problem. However, RRB can spiral into harmful and extreme patterns of behaviour, sometimes also triggering a continuous cycle of action and response between parent/carer and child. For example, a widening gap between the autistic child's behaviour and that of their non-autistic peers or siblings might mean parents/carers or other adults in the child's life try to limit the child's access to their preferred RRB. This inadvertently can lead to more effortful control from the child on their environment with the risk that the RRB becomes entrenched and the child even less willing, for example, to try new foods or access new experiences. In addition, as children grow older increasing social, academic and sensory demands in their environment, together with the inevitable transitions from home to nursery or nursery to school, expose the child and family to new experiences likely to disrupt existing routines. Alongside these developmental shifts, a range of sensory reactivities can be associated with repetitive and restricted patterns of behaviour, as when children self-restrict their diet to food with specific colours or textures. All these different situations require people around the autistic child – especially their parents/carers – to understand and respond to their child's RRB in ways that promote understanding and facilitate autonomy and development.

In young children (aged approximately 3–9 years) irrespective of whether their neurodevelopmental progress is typical or atypical, there is a period of rapid brain maturational growth (during a time of plasticity/rapid learning and change).[18] This period therefore presents an ideal window of opportunity to assist parents/carers to learn how to understand, anticipate and redirect their child's emerging functionally impactful RRB, before they become entrenched and limiting. For all these reasons, it is important to support parents/carers of young autistic children to understand how to manage functionally impactful RRB and so help their child develop a more flexible range of behaviours and constructive ways to deal with the demands of their world.

The role of the family system

There is emerging evidence for the benefit of parent/carer-based interventions in young autistic children, although to date this research has focused on social communication interventions.[19–21] However, parent/carer mediated programmes may be an especially appropriate intervention modality for RRB. Parents/carers need to know that many RRB might be ignored, or cultivated, as a mechanism of self-regulation and a source of enjoyment. In the case of RRB with serious immediate or long-term negative consequences, carefully implemented limit-setting, interruption or redirection may be appropriate. Functional analysis training (a core component of Understanding Repetitive Behaviours;

URB) can support parents/families to begin to understand the environmental triggers and purposes of their child's RRB. They can make use of this understanding to consider if, when, where and how to help their child develop alternative strategies and techniques to manage negative experiences across a range of everyday contexts.

We propose that there are three key stages/steps that need to be incorporated into an intervention to help parents/carers recognise, understand and manage their child's functionally impactful RRB. These steps are included in the URB intervention.

1. Help parents/carers understand why their child may engage in a particular behaviour and, in particular, to identify which of those behaviours are outward signs of distress and/or are most likely to have a functional impact.
2. Enable parents/carers to recognise and understand the way in which their child's RRB may be an outward expression of distress in response to situational stressors, such as anxiety related to change, or sensory reactivity. These relationships will be mediated by the child's social communication difficulties (the other key diagnostic domain for ASD) and cognitive ability.
3. Support parents/carers to identify and apply developmentally appropriate strategies for responding to selected, functionally impactful RRB, including by adjusting or limiting situational stressors. Given the important function that even functionally impactful RRB may have for autistic children, as a way to manage acute stress and distress, it is critical that any intervention which aims to reduce the consequences for the child of these functionally impactful RRB provides opportunities for the development of an extended repertoire of positive coping strategies to deal with the stressors that may trigger a particular RRB.

The URB intervention aims to work with and alongside parents/carers rather than directly with the young child, as parents/carers have unique in-depth knowledge of their child's development and behaviours across a range of settings, and how the child's everyday environment and experiences might be adapted. For example, by providing parents with information and understanding about RRB they may, with practice, be able to reduce background anxiety or support their child to extend their behavioural repertoire in different contexts. Furthermore, we anticipate that providing parents/carers with the skills to understand their child's functionally impactful RRB will have a beneficial effect on parental well-being and family resilience by increasing their sense of competence, reducing stress and improving family cohesion. This in turn will have benefits for the child.

To our knowledge, this study is the first large-scale randomised controlled trial (RCT) of a parent/carer group intervention focused on functionally impactful RRB in autistic young children.[22] To date, the majority of the research interventions for RRB come from single case behavioural studies and while these small-scale studies offer some early emerging evidence of success, limitations include implementation at specialised centres, and highly individualised delivery with expert clinicians.[6]

The URB intervention, if found to be effective, has the potential to extend the range of early interventions available to meet the needs of young autistic children and their families, ensuring the best use of therapeutic resources and reducing the risk that functionally impactful RRB may cause serious harm. Effective early interventions for young autistic children will reduce the longer-term requirement for more specialist services, increasing families' independence from services and thus lowering (NHS) costs.[23] There is increasing impetus among families, professionals, NHS priorities and commissioning documents for research findings on effective and cost-effective early interventions to inform practice, and for effective interventions to be incorporated into the range of available services for young autistic children and their families.

The Autistica/James Lind Alliance[24] identified support for parents/carers to care for and understand their autistic child as amongst the top 10 research priorities for autism research in the future. The National Institute for Health and Care Excellence (NICE)[25] acknowledged the encouraging emerging, but limited evidence base, for young autistic children targeting social communication, but highlighted the absence of specific treatments for young children with functionally impactful RRB that can be so disruptive of individual development and family life. Parent-mediated interventions have the unique advantage of enabling parents/carers to capitalise on opportunities in everyday situations to provide learning experiences. Building on these real-world opportunities may also facilitate generalisation of the child's learning across contexts. Achieving functional change in the context of the child's life and everyday experiences is a priority for the autism community and a key challenge for autism intervention research.

Aims and objectives

The aim of this study is to build on our successfully completed feasibility and acceptability trial[22,26] by evaluating the clinical and cost-effectiveness of the URB parent/carer group intervention compared with a psychoeducation parent/carer group (equivalent to current best practice), in a fully powered two-arm, assessor-blinded, multicentre, individually RCT. Our feasibility and acceptability study showed that parents/carers were willing to be recruited and randomised, and that the format and content of the URB group and the research procedures were feasible and acceptable. Recruitment and retention rates were encouraging: 89% retention (from baseline to final 6-month follow-up assessment), with an attendance rate of 90% at the parent/carer group sessions. The pilot study also examined variability in the proposed outcome measures and provided preliminary evidence of treatment effect.[22] However, given that the feasibility and acceptability study was a single-centre study, we have adopted conservative assumptions throughout as we are mindful that success in a single-centre study may be hard to replicate in a multicentre study.

We predict that supporting parents/carers to recognise, understand and learn to respond to their child's functionally impactful RRBs will result in a reduction in functionally impactful RRBs, and a downstream increase in children's social participation and learning. Furthermore, working with parents/carers will have a beneficial effect on parent/carer well-being by increasing their sense of competence, reducing stress and improving family cohesion.

The trial objectives are to:

1. Compare the clinical effectiveness of the URB intervention for NHS community clinical practice with psychoeducation for the management of functionally impactful RRB in autistic children at 24 and 52 weeks follow-up.
2. Assess the cost-effectiveness and cost consequences of the URB intervention compared with an autism parent/carer psychoeducation group at 52 weeks follow-up.

Chapter 2 Method

Summary of trial design

This study is a UK three-site, two-group RCT of a parent/carer group programme to address functionally impactful RRB in autistic children. Families were randomised at each site to receive either the 8-week URB parent/carer group programme or the 8-week Learning About Autism (LAA) parent/carer group programme, equivalent to best current practice and operating as an 'attentional control' for time spent in a parent group and attention from autism professionals and other parents/carers. Assessments were administered on entry (baseline) to the trial, at the end of the eight parent/carer group sessions (10 weeks), at 24 weeks primary end point and at the 52 weeks follow-up. The study is a phase 3 superiority trial, with a parallel group design in which each family is randomised 1 : 1 to one of the two parent/carer group programmes.

Parent/carers were randomised 1 : 1 to receive either the URB programme or the LAA attentional control programme. The study was conducted through three research sites:

- Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust (CNTW)
- NHS Lothian
- Tees, Esk and Wear Valleys NHS Trust (TEWV)

Understanding Repetitive Behaviour programme

Understanding Repetitive Behaviour is a manualised programme designed to help parents/carers of young autistic children to recognise, understand and learn how to support their child's functionally impactful RRB. It is an 8-week programme designed to be delivered by community-based professionals with knowledge and experience of working with young autistic children and their families, who have been trained to deliver the URB programme. Each weekly session lasts for 2 hours (total duration of group programme is approximately 16 hours).[2]

Each parent/carer is provided with an URB folder with copies of the weekly session slides and materials and individual support to identify sensitive approaches to address functionally impactful RRB. 'At home' activities are set each week for parents/carers to complete with their children between sessions. Parents/carers are asked to keep a diary of these activities. The opportunity to identify and practise new ideas outside of the clinic setting is considered to be important for investigating how best to generalise the approach into different settings for each child and family.[2]

Understanding Repetitive Behaviour supports families to begin to recognise and understand their child's functionally impactful RRB, differentiate these behaviours from those that do not impact function, consider how they respond and the impact that their responses may have on their child and the behaviour. Firstly, parents/carers recognise and consider what the function might be of the identified functionally impactful RRB for their child in a particular context. For example, if a child responds negatively (e.g. becomes distressed or physically aggressive) to the front door being opened or the vacuum cleaner being turned on, then the function of the child's behaviour may be to reduce or remove the level of uncertainty or the aversive sensory input. Alternatively, some RRB may provide an enjoyable pastime for the child. Functional analysis principles help parents/carers to understand their child's RRB and to decide whether, as well as how, to intervene. The URB programme supports parents/carers to develop alternative strategies and techniques to reduce any negative impact from their child's functionally impactful RRB across a range of everyday contexts. Strategies might include providing advance warning about unpleasant stimuli (such as vacuum cleaning) and a place to hide away for the duration; providing designated spaces for collections to be laid out undisturbed, while allowing other family members to move about the home freely; gradually building up tolerance to wearing certain items such as a coat during colder days; providing alternative items for a child who likes to touch people's hair to hold or touch such as a doll; limiting the purchasing of new additions to collections to a specific frequency or context; providing alternate foods not surreptitiously, but overtly and with no insistence to try them. Such strategies are designed to provide autistic children

with ways to manage uncertainty, cultivate interests and engage with the world safely and without resorting to extreme restriction as a coping strategy.

Parents/carers have opportunities for both individual support with the professionals trained to deliver URB and group learning. In weeks 2 and 7, they meet the group leaders individually to select a target functionally impactful RRB to focus on during the group and to apply new knowledge and practise the new skills they are learning, thus ensuring that strategies are individually tailored for each child and are developmentally appropriate.[2]

There are also opportunities for mutual learning and sharing of ideas. As part of the URB programme, parents/carers are asked to video their chosen/target functionally impactful RRB at home. These videos are then shared in the sessions, allowing parents/carers opportunities to discuss how they are recognising and learning to support their child. This fosters opportunities for parents/carers to learn from and support each other as they share their experiences as parents/carers of young autistic children. These videos are never shared outside the group.[2]

Psychoeducation Learning About Autism parent group (attentional control)

The LAA group acts as an attentional control for time and attention. LAA comprises eight 2-hour parent/carer group sessions focusing on understanding autism. The groups offer parents and carers psychoeducation on understanding autism and what that means for their child, such as helping them to understand their child's social communication difficulties and behaviour in different environments. It also provides advice and guidance on strategies and approaches for dealing with, for example, behaviours that parents/carers find functionally impactful. There are opportunities for mutual support and sharing of ideas with other parents/carers, thus increasing parents' and carers' understanding, confidence and responsiveness to their child's patterns of communication and interaction. This is equivalent to current best practice. It does not include any specific information about the role and functions of RRB, functional analysis and tailored strategies to manage functionally impactful RRB.

Study settings and sites

Both the URB and LAA programmes have been developed to be delivered in local community settings by early years professionals experienced in working with young autistic children and their families. The parent/carer groups took place in community settings in different geographical locations across the three sites in CNTW, Lothian and TEWV [or remotely via online delivery as a consequence of coronavirus disease 2019 (COVID-19) restrictions post March 2020]. We have carefully considered the level of professional expertise necessary to deliver both the URB and LAA programmes effectively and safely. Both programmes were delivered by staff with experience in working with young autistic children and their families, with appropriate training and supervision.

Participants

Parents and carers aged 18 years and older were eligible for study entry if their child met the following criteria:

1. Aged 3 to 9 years 11 months at the time of consent with a clinical diagnosis of autism or ASD across a range of functioning levels and abilities (verbal and nonverbal).
2. Parents/carers had to have sufficient spoken and written English to provide written informed consent and complete the assessments, including being able to identify one or more functionally impactful RRB and participate in the group-based programme.
3. Parents/carers had to be willing to be randomised and attend all the group sessions for the allocated arm of the study and agree to maintain their child's current medication regime up to 24 weeks (unless change is advised by the child's clinician) and to agree not to participate in any other trials while involved in the trial up to 24 weeks.

Parents/carers were not eligible for study entry if their child met the following criteria:

1. no clinical diagnosis of autism or ASD;
2. no functionally impactful RRB that could be identified;
3. currently taking part in another parent/carer group-based programme trial; or
4. had a sibling already taking part in this study.

Furthermore, parents/carers with a severe learning disability or a significant mental health disorder that would interfere with their ability to take part in a group-based programme were not eligible to participate.

Recruitment

Potential participants were identified through the three research sites, as well as through Participant Identification Centres (PICs). Clinicians were provided with information on the URB study and asked to introduce the study to families. This might be in person at a clinic appointment, in a community setting/school or by letter. Clinicians gave potential families copies of the patient information sheet (PIS) and an expression of interest (EoI) form to be returned by the clinician or the family to the research team using the stamped addressed envelope provided. Families were also invited to take part through diagnostic clinic databases and research databases such as ASD database-UK (ASD-UK). The local Clinical Research Network (CRN) at each site assisted with recruitment.

Interested parents/carers were asked to complete and return to the research team an EoI form. The research team then contacted parents/carers who were interested in hearing more about the study to arrange a meeting or phone call to discuss the study, what participation involves, answer any questions they may have, and obtain written informed consent via an informed consent form (ICF).

Newsletters summarising the progress and findings of the study were designed by the research team and parent/carer advisers. These were sent to families and local professionals who had taken part in recruitment and supported the study during the trial, to support retention.

Screening

Eligibility procedure

- Where there was any doubt, after first appointment or after all assessments, eligibility was discussed by the research associate (RA), the principal investigator (PI) at each recruiting site and other members of the senior research team.
- If the participant met the eligibility criteria, the RA sent a letter/e-mail thanking the parents/carers for participating in all the assessments, and to confirm eligibility and that the family had been put forward for randomisation. A separate letter was sent to the GP/referrer to notify them of this.
- If the child did not meet the eligibility criteria, the RA or the PI contacted the family to discuss.
- The RA or the PI also informed the referrer if the child did not meet the eligibility criteria.

Consent

At each recruiting site, once the EoI was received by the research team, parents/carers were contacted directly and an initial appointment with the RA made at a mutually convenient time to discuss the details of the information sheet and the purpose of the study. Parents/carers were given the opportunity to discuss any questions or concerns they might have to ensure that they were fully informed about the study. They were then asked to give informed consent at this initial contact appointment. A minimum of 24 hours was afforded for consent.

Randomisation

Randomisation was done through the Sealed Envelope (www.sealedenvelope.com/) web-based randomisation service. Randomisation was at child level using equal allocation ratio. Each parent/carer was automatically considered in their child's randomisation group. We opted for child-level randomisation instead of parent/carer-level randomisation because the primary outcome is at child level, and it is important to account for child-level characteristics that can affect the primary outcome.

Age (3–5 years vs. 6–7 years vs. 8 to 9 years 11 months), gender (male vs. female) and ethnicity (white vs. non-white) were accounted for in allocating children to either the URB group or the LAA comparison group. Given the prevalence of RRBs across the autism severity range, severity was not accounted for in allocating groups. Due to the nature of the study and the few factors (age, gender and ethnicity) that needed to be accounted for in the randomisation, a minimisation scheme instead of stratified randomisation was used to minimise sample fragmentation due to the number of strata and to avoid accidental imbalance between the URB group and the LAA comparison group. Unlike stratified randomisation, minimisation works towards minimising the total imbalance for all factors together instead of considering mutually exclusive subgroups.

The clinical leads at each site informed the families of the outcome of randomisation by telephone and the randomisation decision was also confirmed by letter. This was also recorded in the child participant's NHS patient record.

Participant allocation

Two hundred and twenty-seven parents/carers of young children (aged 3 to 9 years 11 months) with a clinical diagnosis of ASD across a range of functioning levels and abilities (verbal and nonverbal) were recruited through child health and child and adolescent mental health teams across three sites (CNTW, Lothian and TEWV). Following recruitment, the first 25 children were randomly allocated to receive the URB parent/carer group programme or the LAA psychoeducation group. For the minimisation scheme, the first child was randomly allocated to either the URB group or the LAA group using simple randomisation with 50% equal probability. The remaining 202 children were allocated to either the URB group or the LAA group by minimising marginal imbalance between the two groups (based on age, gender and ethnicity) and a prespecified probability of 10%. For example, if the second child to be randomised was a male, 3–5 years and from white background, suppose a white male child, aged 3–5 years was already allocated to the URB group. Although allocating the second child to the LAA group would lead to less overall imbalance score, he/she might be assigned to the URB group because of the prespecified probability of 10% to conceal the allocation.

Blinding

The RA at each of the three recruiting sites was based in a separate location (usually university premises) to the group leaders and remained throughout the study 'blind' to the group status of all the recruited children and families in the trial. The RAs were trained to reliability in all baseline characterisation and outcome measures. For each recruited child and parent/carer(s), once informed consent and all the baseline measures were completed and scored and eligibility confirmed by either the site RA or PI (see Eligibility procedure above), the participants were randomised. The site clinical leads were informed (in writing via e-mail) of the outcome of the randomisation. The parent/carer participant then received a telephone call and a letter from the clinical lead at each site confirming the randomisation outcome. The RAs were not informed of the randomisation outcome. Then prior to and at each subsequent follow-up visit, parents/carers were reminded not to disclose to the RA the child/family randomisation status. This means that throughout the trial the RAs remained blind to the randomisation status of all study participants.

Unblinding

Participants, group leaders and clinical leads were not blind to participant group allocation. All other members of the research team at each site were blinded. As such, there was no anticipation for the need of unblinding while the study was in progress. However, in the unlikely event of a RA being inadvertently unblinded to the randomisation status of an individual child, this was recorded on the trial database and the site clinical and research leads were informed. Where possible, future assessments with this participant were carried out by an alternative blinded RA.

Patient and public involvement

The URB programme and the RCT study protocol have been developed jointly in partnership with parents/carers of young autistic children through two development parent/carer groups and a pilot feasibility and acceptability study.[22] The pilot study funded by National Institute for Health and Care Research (NIHR) Research for Patient Benefit (RfPB) programme included end-of-treatment participant focus groups led by trained parent/carer(s). The trained parent/carer focus group leaders followed a semistructured topic guide with the aim of considering three key areas of interest: experiences of participating in a research study, opinions about the URB programme and the impact of the URB programme on the participants, their children and the family. Fourteen parent/carer participants attended the focus groups. Participants were positive about URB, and they particularly liked the group-based format. Most participants reported that they had little knowledge of RRB before attending the programme and that it had had a positive impact on them, their children and their family. The two parent/carer focus group leaders have successfully co-authored a peer-reviewed publication on the findings from the focus groups.[26]

We had two parent representatives [one from the National Autistic Society (NAS) and one from our development work] on the URB RfPB Steering Committee. The findings from the NIHR RfPB pilot study have been disseminated by several of the co-applicants (including one of the parents who took part in the study) at local and national parent/carer and practitioner meetings/conferences.

Furthermore, we consulted with Professor Helen McConachie, Newcastle University regarding the design of our programme following the NIHR Health Technology Assessment (HTA MeASURe systematic review of tools to measure outcomes for young children with ASD).[27] Professor Ann LeCouteur, Professor Jacqui Rodgers and Deborah Garland were co-applicants on this review.

We have continued to involve the UK organisation NAS in the research process, from the design of the LAA psychoeducation comparison group, to the planning and management of the delivery of the RCT study to the dissemination of research findings. We have also continued to work collaboratively with parents/carers throughout the design and conduct of the current RCT informed by INVOLVE guidance on training, support and remuneration of expertise to ensure parents/carers are included in a meaningful way. Two parent advisers were Trial Steering Committee (TSC) members for the pilot study and have continued to advise on recruitment and retention strategies and implementation of study procedures. We have convened a new parent advisory group, including autistic parents, to provide additional consultation to the research team with respect to interpretation of findings and dissemination.

Training and fidelity

All URB group leaders and site clinical leads attended a one-day URB training course covering how to use the training manual and the materials for each of the eight 2-hour weekly sessions, planning for homework tasks and supporting parents/carer in using the technology. Each group leader learnt about group processes and gained skills to deliver the manualised programme in a participatory style, in combination with strategies to personalise the programme for each parent/carer. The senior trainer (LD) alongside the chief investigator (VG) delivered the introductory training course and also visited each site as each new group had started. Furthermore, to ensure that the programme was being delivered to the families as intended with high fidelity to the manual, the senior trainer, alongside the local clinical lead, also

undertook weekly supervision of group leaders at each site and monitored the quality of parent/carer group sessions by video, providing timely feedback to group leaders.

Group leaders delivering the LAA parent/carer group attended a one-day training course specifically designed for this study to ensure that they were trained in the skills needed to deliver the programme. This course had been designed by the NAS and was delivered by DG.

All parent group sessions in both arms of the trial were recorded, to facilitate opportunities for supervision of the group leaders and to provide access to a random sample of recorded sessions across all sites for the independent evaluation of fidelity. The fidelity checklists for each programme (URB and LAA) measured (1) the fidelity to the delivery of the programme (i.e. session structure, techniques and therapeutic components) and (2) the fidelity to the content of the programme.

Four independent raters were trained to use the URB and LAA fidelity coding checklists. The independent raters were randomly allocated 10% of the recorded parent/carer group programme sessions.

Parent/carer attendance at group sessions was recorded and monitored. Parents/carers who missed a URB session were contacted by a group leader to provide a brief overview of the session and handouts for that session were also posted out. For both groups (URB and LAA), session attendance and receipt of other programmes outside of the protocol were monitored.

Avoidance of contamination

There were separate clinical and research leads at each site and separate training and supervision structures. Researchers were located separately from staff involved in delivery of the URB and LAA groups. Research interviews and assessments were conducted mostly at home visits (or via telephone post COVID-19 restrictions being implemented in March 2020). All parents/carers were reminded prior to every contact with research staff not to talk about group allocation. Further, we also considered additional issues around potential contamination of the active attentional control LAA group, by ensuring that the LAA families were not on the clinical NHS caseload of the URB programme group leaders. The clinical and research leads in the trial were experienced in studies of this type and therefore were able to take additional steps, if needed, to discern and avoid any potential risk of contamination bias.

Outcome measurements

The clinical effectiveness of this programme was assessed by measuring whether children show overall improvement using the Clinical Global Impression - Improvement scale (CGI-I; primary outcome) at 24 weeks (primary end point) after the URB programme compared to the children whose parents/carers had attended the LAA group. There were several secondary outcomes that were measured at the end of the programme (10 weeks) and at 24 weeks and 52 weeks follow-up to capture independent (blinded researcher), teacher and parent-reported changes. These included change in functionally impactful RRBs. Parent/carer questionnaires also provided information on child RRB, child participation and daily living skills, parent/carer stress, self-efficacy and impact on family life. Parents/carers were aware of group status, but teachers and the primary outcome assessors (RAs) were blind to group allocation.

Baseline characterisation and outcome measures

The following baseline measures were collected:

- **Demographics**: a bespoke demographics tool was designed for the study. Parents/carers were asked about their child's age, gender, type of nursery/school provision, diagnosis and ethnicity, current medication and additional

diagnoses. Information was also obtained on parent/carers' level of education, employment status, family structure, and if they had attended any previous course or intervention programmes for autistic children.

- **Autism Diagnostic Observation Schedule-2 (ADOS-2):**[28] this is a standardised observational assessment undertaken by a trained examiner. It is a semistructured set of play and social communication activities that involves both specific activities and spontaneous social interaction between the examiner and the child. It is designed to elicit a range of behaviours including social communication skills and difficulties. Children were assessed with the developmentally appropriate Module (Module 1, 2 or 3 according to language level and chronological age). During the ADOS-2, elements of the child's behaviour are observed and scored in two domains: social affect and RRB. The scores for the domains are combined into a total score. The total score is then used to derive a comparison severity score ranging from 1 to 10. Comparison scores of 1–2, 3–4, 5–7, 8–10 indicating minimal to no evidence, low, moderate and high levels of autism spectrum related symptoms, respectively. From March 2020 onwards, ADOS-2 assessments were not able to be undertaken once national governments' and NHS COVID-19 restrictions were implemented.
- **Social Responsiveness Scale – Second Edition (SRS-2**):[29] The SRS-2 (preschool form or school form according to child's chronological age) is a 65-item questionnaire measure of the social impairments that are characteristic of ASD. It is completed by the parent/caregiver. Interpretation is based on a single score (total score) reflecting the sum of responses to all questions, which serves as an index of severity across the autism spectrum. A total T-score of 76 or higher is considered severe and strongly associated with clinical diagnosis of autism. T-scores of 66 through to 75 are interpreted as indicating moderate difficulties in reciprocal social behaviour that are clinically significant and lead to substantial interference in everyday social interactions, whereas T-scores of 60–65 are in the mild range and indicate mild to moderate deficits in social interaction. T-scores of 59 and below are considered to be within typical limits and are generally not associated with a clinical diagnosis of ASD.

Primary outcome measure

Clinical Global Impression – Improvement scale:[30] The CGI-I provides a standardised framework for clinicians to assess how much symptoms have improved or worsened relative to the child's baseline state using a 7-point scale (1 – very much improved; 2 – much improved; 3 – minimally improved; 4 – no change; 5 – minimally worse; 6 – much worse; or 7 – very much worse). Researchers and clinicians, blind to group allocation, were trained to reliably and independently rate global improvement over the 24 weeks (from baseline to primary end point), using all available child information from baseline, and week 24 [SRS-2 (baseline only), Vineland Adaptive Behaviour Scales 3 (VABS-3), target behaviour vignettes (TBVs), parent/carer and teacher Repetitive Behaviour Questionnaire – 2 (RBQ-2)]. In line with other published studies, ratings of 1 (very much improved) and 2 (much improved) are regarded as clinically significant 'improvement' and were used to define the binary outcome of improvement or no improvement for each child for the comparison of the URB intervention group and the LAA attentional control group at the primary end point.

For 10% of participants, the CGI-I score was independently rated by a second trained researcher to assess inter-rater reliability.

Secondary child outcome measures

Measurement of RRB – Target Behaviour Vignette:[31] As part of the baseline characterisation, parents/carers were asked to identify two functionally impactful RRBs. Parents/carers were asked questions about the duration, impact and possible triggers and functions of the functionally impactful RRB using a standardised semistructured interview. The protocol for measuring change in the parent/carer defined TBV was originally developed by The Research Units on Paediatric Psychopharmacology and Psychosocial Intervention Programmes (RUPP Autism Network). At each outcome assessment point, the parent/carer completed the follow-up version of the standardised semistructured interview. The parent/carer responses at each time point were audio recorded and contributed to a vignette written by the RA (blind to randomisation status). Audio files were stored as a password-protected secure file with anonymised file name (using study ID code). In keeping with the procedure developed by RUPP, after all data were collected, a panel of blinded autism experts independently rated change in each target behaviour and change in relation to the impact on the family.

Three pairs of vignettes [comparing each time point (10; 24; 52 weeks) to baseline] were rated for each child on a 9-point scale of improvement/deterioration (1 – very much improved; 2 – markedly improved; 3 – definitely improved; 4 – equivocally improved; 5 – no change; 6 – equivocally worse; 7 – definitely worse; 8 – markedly worse; 9 – disastrously worse). A positive response (also described as a 'responder') was defined as a rating of 3 or less.

Measurement of RRB – Repetitive Behaviour Questionnaire – 2 (RBQ-2):[32] The RBQ-2 is a 20-item questionnaire completed by parents/carers that measures the frequency and intensity/severity of RRB known to occur in both autism and typical development. The RBQ-2 was developed using items from the original RBQ[33] and the diagnostic interview for social and communication disorders (DISCO). The RBQ-2 has been reported to be a valid measure of RRB in a sample of children with ASD aged 2–17 years, showing good internal consistency.[34] Scores range between 1 and 3 and a higher score is indicative of more RRB.

The Teacher Repetitive Behaviour Questionnaire – 2 (Teacher RBQ-2):[35] This is the corresponding version of the parent/carer RBQ-2 for completion by teachers/teaching assistants. It measures the frequency, intensity and severity of RRB in a classroom setting. Scores range between 1 and 3 and a higher score is indicative of more RRB.

Vineland Adaptive Behaviour Scales 3 (VABS-3):[36] The VABS-3 measures aspects of the child's level of adaptive functioning. The parent/carer rating form was used. This focuses on four domains of everyday functioning: communication, daily living skills, socialisation and motor skills (0 for never, 1 for sometimes and 2 for usually or often). The assessment was undertaken with parents/carers by a trained researcher. The domain composite scores provided an adaptive behaviour composite (ABC). A higher score indicates a greater level of ability.

Secondary parent outcome measures

Secondary parent/carer measures were completed by the parent/carer who attended group sessions in both arms or, if both parents/carers planned to attend sessions, the nominated main parent/carer was asked to complete all parent/carer report measures.

Parent self-efficacy:[37] This 15-item questionnaire completed by parents/carers measures behaviours typically exhibited by autistic children. Parents/carers indicate 'yes' or 'no' to whether the child displayed each of the behaviours in the previous month and then rate their confidence in managing the behaviours on a 6-point scale ranging from 0 (no confidence) to 5 (complete confidence). A mean self-efficacy score is calculated by dividing the total confidence score by the number of behaviours reported as displayed. A higher score indicates more parental self-efficacy.

Autism Parenting Stress Index (APSI):[38] This is a measure of parenting stress specific to core and comorbid symptoms of autism. It was designed to be used to identify areas where parents/carers need support with parenting skills, and to assess the effect of the interventions on parenting stress. Exploratory factor analysis suggested three factors impacting parenting stress relating to core deficits, to comorbid behavioural symptoms, and to comorbid physical symptoms. Psychometric properties are good (e.g. Cronbach's alpha 0.83). A higher score is related to more self-reported parenting stress.

Warwick–Edinburgh Mental Well-being Scale (WEMWBS)[39] is a psychometrically robust parent/carer rated 14-item well-being questionnaire with good internal consistency (Cronbach's alpha 0.89) and test–retest reliability (ICC 0.83). It is recommended by the Department of Health and Social Care as the preferred measure of mental well-being and that it is important to incorporate in parent-mediated studies where parental/carer well-being may impact on child outcomes. A higher score is an indicator of a greater level of parental well-being.

Secondary family outcome measures

Autism Family Experience Questionnaire (AFEQ):[39] This questionnaire was developed to measure the broader impact of an intervention on young autistic children and on their families in terms of participation in everyday activities. It was

commissioned by the Medical Research Council as part of the Preschool Autism Communication Trial[40] and based on focus groups and piloting with parents/carers of young children with ASD to reflect what changes in their lives would 'make a difference'. A lower score indicates a more favourable outcome.

Data collection

Baseline assessment and follow-up measures were collected by RAs blinded to the outcome of randomisation. RAs were trained to high levels of reliability in all baseline characterisation and outcome measures (*Table 1*). All families were allocated a unique number that was used to identify them on all paper assessment forms throughout the trial. All data collected on paper were inputted into a data management system for eventual statistical analysis and all identifying data were stored securely separately. The Clinical Data Management System (MACRO) used for this trial is fully compliant with all regulatory frameworks for research of this nature. Participants cannot be identified from electronic case report forms (eCRFs). The CI or delegated person monitored completeness and quality of data recording in eCRFs and corresponded regularly with site RAs, research leads and PIs (or their delegated team member) with the aim of capturing any missing data where possible and ensuring continuous high quality of data. All study data were treated in accordance with the latest directive on good clinical practice (GCP).[41]

Data management

Data were entered by sites on to the MACRO (Elsevier B.V., Amsterdam, The Netherlands) database and were checked throughout the recruitment period to ensure that the eCRFs were as complete and accurate as possible. There were two types of validation to ensure data integrity: manual and electronic. The following types of checks were performed: range checks, consistency checks, protocol checks and accuracy checks. All issues arising from the checks were queried with site staff. All changes to the data were documented in the audit trail including details of who made the change, when the change was made and why the change was made, to prove data integrity. Essential data will be retained for a period of at least 5 years following close of the trial in line with sponsor policy and the latest European directive on GCP.[41] Data were handled, digitalised and stored in accordance with the Data Protection Act 1998 and the Data Protection Act 2018. In line with General Data Protection Regulations (GDPR), the sponsor was the data controller for this study and Newcastle Clinical Trials Unit (NCTU) was the data processor.

Trial management

The Data Monitoring Committee (DMC) was independently chaired and comprised of a panel of independent members including a principal clinical psychologist and a post-doctoral research associate as well as non-independent members that were part of the Trial Management Group (TMG). Serious adverse events (SAEs), and actions taken, were logged by the senior trial manager (STM) or trial manager (TM) at NCTU and a report presented to DMC. The DMC met once a year to receive reports on recruitment and SAEs. The DMC (which is independently chaired and includes an independent statistician) members evaluated the findings of the internal pilot in August 2019 and submitted a report to the NIHR.

The project also had a TSC with an independent chair and a panel of independent members including a statistician, health economist and two parent representatives as well as non-independent members, from the TMG. The TSC met approximately annually throughout the trial moving to bi-annually during the COVID-19 pandemic (*Table 2*).

The DMC and TSC members, appointed by the funder, were independent of the sponsor and funder and declared no competing interests. The TMG consisted of the CI, co-applicants, and members of NCTU including the TM, STM, clinical trial administrator and data manager, trial statisticians, health economists, members of each site, sponsor and CRN staff.

Throughout the duration of the trial, the RAs discussed any challenges with data collection with research leads at each site and the research team at each site. The RAs were responsible for ongoing review of data completeness and any

TABLE 1 Schedule of events

Procedure	Screening	Baseline	Treatment phase	Follow-up		
			Weeks 1–8	Week 10[a]	Week 24[a]	Week 52[a]
Informed consent	X					
Child and parent demographics[b]	X				X	X
Eligibility	X					
ADOS-2[c]		X				
SRS-2		X				
CGI-I					X	
Parent RBQ-2		X		X	X	X
Teacher RBQ-2		X		X	X	X
TBVs		X		X	X	X
VABS-3		X			X	
Parent self-efficacy questionnaire		X		X	X	X
Autism parenting stress index		X		X	X	X
WEMWBS		X			X	X
Autism family experience questionnaire		X			X	X
CHU-9D		X			X	X
EQ-5D-5L		X			X	X
Resource use questionnaire		X			X	X
Time and travel questionnaire		X				
Randomisation[d]		X				
Weekly programme (URB or LAA)			X			

CHU-9D, Child Health Unity 9D.

a Timing of follow-up assessments was calculated relative to week 1 of the start of the intervention phase. A ± 2-week window is allowable per protocol, but it is accepted that there may be some variability in the timing of assessments.
- 10-week – if collected before 17 weeks.
- 24-week – if collected 17 weeks to 38 weeks.
- 52-week – if collected after 38 weeks.

b Child demographics to include – child age, gender, type of nursery/school, diagnosis, current medications, additional diagnoses, ethnicity, previous programme exposure. Parent/carer demographics to include – level of education, employment status, family structure, attendance at previous courses or programmes relating to children with a diagnosis of ASD. Demographics follow-up form will be completed at weeks 24 and 52 to avoid repetition of information.

c ADOS assessments have only taken place prior to March 2020 due to COVID-19 restrictions.

d Randomisation to take place following completion of baseline assessment.

concerns were discussed with the research team, NCTU and the sponsor, as appropriate. Throughout the latter stages of the trial, the TMG was split into a section specific to site and a core TMG where specific trial items were discussed.

The NCTU were responsible for oversight of the day-to-day running of the trial on behalf of the sponsor. The TM conducted several on-site monitoring visits throughout the course of the trial to ensure that all standards were met according to GCP and any issues or concerns were identified and rectified. Source data verification and review of the medical notes to ensure safety information was captured appropriately was also conducted. Throughout the pandemic, monitoring visits were conducted with one conducted remotely.

TABLE 2 The highlights and decisions of TSC/DMC meetings

Meeting	Date	Highlights
DMC	11 October 2018	Study set-up: – role of DMC – review of study documentation – committee report discussed
TSC	26 November 2018	Study set-up: – role of TSC – review of study documentation – committee report discussed – overview of trial
DMC	15 July 2019	Overview of recruitment, slow to start, recruitment strategies discussed. Staffing and new RA on board
TSC	13 August 2019	Recruitment strategies, parent feedback
DMC	August 2019	Received approval to progress to main trial
	12 November 2019	Extension to recruitment discussion by 3 months, concerns over number of withdrawals, power
TSC	4 December 2019	Progress on recruitment monitoring, report overview
DMC	15 February 2020	Progress on recruitment, first draft of SAP, monitoring visits and violations. Report overview
TSC	31 March 2020	COVID-19 – amendments to be put in place and mitigations to ensure trial can continue
DMC	06 July 2020	Amendments to cover additional question in target interview questionnaire and COVID-19 adaptations to continue the trial. A further extension to recruitment for an additional 3 months
TSC	24 August 2020	Formal request from funder to submit 8-month extension. Adaptations to trial for COVID-19, parent feedback positive, discussion around events of special interest
DMC	5 October 2020	Discussion around costed extension for 8 months due to COVID-19 pandemic – 4 months at a cost to funder. Data need adjusting to be clearer within closed report. Final recruitment figures
TSC	15 December 2020	Discussion around costed extension for 8 months due to COVID-19 pandemic – 4 months at a cost to funder. Data need adjusting to be clearer within closed report. Final recruitment figures
DMC	25 May 2021	Closed to recruitment, focus on data collection and follow-ups. Approval of study extension to 31 March 2021. Protocol paper published. Number of staff changes
TSC	17 June 2021	Analysis particularly primary outcome, data lock, timelines
Joint DMC/TSC	09 May 2022	Results reveal

SAP, statistical analysis plan.

Statistical methodology

Sample size

We planned to approach approximately 325 families and expected to randomise 250 families (125 randomised to each arm). Assuming 5% type I error, 90% power, 10% intra-group correlation and equal allocation ratio, 224 families (an average of 8 families per parent/carer group) were required to detect 20% improvement rate between the URB programme and LAA group at 24 weeks. Allowing for an attrition rate of 12%, 250 families were expected to be randomised. The 10% intracluster correlation was based on review of group programmes in education trials.[28] Sample size was calculated in R using n4props in Sample Size Estimation Functions for Cluster Randomised Trials (CRTSize) package.[42]

Statistical analysis plan

The analysis of the primary outcome at 24 weeks used generalised estimating equations (GEEs) with binomial distribution and logit link. Exchangeable working correlations were used to account for the clustering of children by parent/carer groups. The continuous secondary outcomes were first analysed at 24 weeks using a difference-in-difference model based on linear mixed-effect model accounting for paired data (at baseline and at 24 weeks) per child and clustering of children by parent/carer groups. The same model was applied to the data at week 52, which was analysed as longitudinal data incorporating data at baseline and 24 weeks. All binary or categorical secondary outcomes were analysed using GEE. We also performed safety analysis and sensitivity analysis for missing data and assessed the impact of the COVID-19 pandemic on primary and secondary outcomes.

All continuous variables were summarised using *n* (non-missing sample size), mean, standard deviation (SD), minimum and maximum. The frequency and percentages (based on the non-missing sample size) of observed levels were reported for all categorical data. All summary tables were structured with a column for each trial arm, and they are annotated with the total population size relevant to that table/treatment, including any missing observations. Primary analysis according to CGI-I at 24 weeks was performed using GEE with binomial distribution and logit link. We accounted for clustering of children by parents' groups using exchangeable working correlation assumption and the analysis used the full analysis population and intention-to-treat (ITT) principle. We also adjusted for the minimisation variables [age (3–5 years, 6–7 years and 8 to 9 years 11 months), gender (male vs. female) and ethnicity (white vs. non-white)], as this has been shown to improve efficiency of statistical inference.

As part of sensitivity analysis for the primary outcome, we evaluated the impact of missing data using the so-called weighted GEE [weighted generalised estimating equations (WGEE)].[43] This method works under the assumption of missing at random (MAR) missing data process, which is often the basis for carrying out multiple imputation of missing data. The main idea of WGEE is to supplement the outcome with a predictive model for the missing rates conditional on the observed ones. Due to insufficient observations, the subgroup analyses for age categories were not conducted. For the TBVs we compared change scores between the trial arms at 10, 24 and 52 weeks. The prespecified analysis is GEE, in a similar version to the primary analysis. Due to model non-convergence, we reduced the level of the models and analysed the data using logistic regression, with effects of interest captured using odds ratios (ORs). All the models were adjusted for the minimisation variables as prespecified. For the remaining secondary outcomes, we prespecified an alternative model to analysis of covariance (ANCOVA) using the linear mixed-effects models for mean difference as the change from baseline in the questionnaire measures with continuous scores. The latter has been shown to produce robust standard errors. The model is specified such that baseline values are part of the outcome vector, constraining the baseline across trial arms. In this formulation, the inference is not based on the point estimates of trial arms but the interaction between the trial arms and follow-up time points. All other secondary outcomes were analysed using appropriate models using the ITT principle. We also noted that the per-protocol population was essentially the same as full analysis population because in both all participants met the inclusion and exclusion criteria in the protocol, received the treatment group, completed 24 weeks follow-up, and did not deviate from the protocol as agreed with the TSC. Since there was no clear cut-off point to define adherence to the programme (dosage of URB), complier average causal effect (CACE) analysis was not performed, instead we provided descriptive statistics on attendance rates in parent/carer groups in the *Results* chapter.

The impacts of the COVID-19 pandemic that started during the course of this trial were assessed on the primary outcome and TBV using difference-in-difference models between the participants who had their 24-week (primary end point) visit pre and post COVID-19 lockdown starting on 23 March 2020 (see *Appendix 4*). This was specifically done by creating an indicator variable which takes values of 1 ('post lockdown') for data collected after 23 March 2020, and values of zero ('pre lockdown') for the data collected before the lockdown. Although this study was not powered to detect interactions, a significant interaction between lockdown indicator and URB programme status would indicate that the outcomes differ between the pre- and during lockdown period.

Recording and reporting serious adverse events

For the purposes of this trial, serious adverse events [adverse events which met the criteria for seriousness (SAEs)] were captured for the parent/carer and child participants. SAEs were captured from the start date of participation in either LAA or URB until the follow-up assessment at week 24.

As soon as a site suspected that a SAE might be related to the trial intervention, they contacted the TM immediately. The reporting time frame started at day 0 when NCTU was in receipt of a minimum set of information:

- sponsor trial reference and trial name (sponsor reference)
- patient trial number and date of birth
- parent or child participant
- name of intervention
- date of notification of the event
- medical description of the event
- date and time of the onset of the event (including event end date if applicable)
- causality assessment
- seriousness of the event, particularly if life-threatening or fatal
- an identifiable reporter (e.g. PI).

This information had to be provided on the trial-specific SAE form. The site was expected to fully cooperate with NCTU in order that a full and detailed report could be submitted to the NHS Research Ethics Committee (REC) within the required timelines.

Events of special interest

As well as collecting and ensuring SAEs were reported, events of special interest (ESI) were also collected. An ESI was defined as any event relating to child well-being and family/life difficulties which was not expected and not anticipated in 'normal day-to-day life' but was not a physical medical event. ESIs were recorded for both the parent/carer and child participants from the start date of either URB or LAA until the follow-up assessment at week 24.

Compliance and withdrawal

Participants had the right to withdraw from the trial at any time without having to give a reason. Investigator sites tried to ascertain the reason for withdrawal and document this reason within the CRF and the child participant's medical notes. For participants who withdrew, data captured up until the point of withdrawal were retained, unless participants withdrew consent.

The clinical lead at each site could discontinue a participant from the trial at any time if they considered it necessary for any reason including but not exhaustive to the examples below. This decision was initially made at each site but discussed with the wider research team if necessary. The CI and NCTU were then informed:

1. symptomatic deterioration
2. parent/carer withdrawal of consent
3. significant protocol deviation or non-compliance
4. investigator's discretion that it is in the best interest of the child and/or parent/carer to withdraw
5. an adverse event that requires discontinuation of the trial programme or renders the child or parent/carer unable to continue in the trial
6. termination of the clinical trial by the sponsor.

Participants were classed as enrolled in the trial once randomised. Participants who withdrew from the trial after randomisation were not replaced.

Changes to study design

Several amendments were made throughout the course of the trial. *Table 3* depicts the substantial amendments and their summary.

TABLE 3 Significant amendments implemented within the trial time frame

SA1	REC Approval 9 October 2018	Update to several documents including parent/carer EoI form, eligibility letter, randomisation outcome letter, information for referrers, Vineland Adaptive Behaviour Scale, 3rd Edition, Baseline Demographics Form
SA2	REC Approval 4 February 2019 (reissued)	Inclusion of PIC sites. Consent form – parents/carer currently consent to video recording. As one of the trial assessments (TBV) is more suitable for audio recording, this has been updated to include consent for audio recording. Also updated to include consent to receive newsletters. PIS updated to reflect assessment that will be audio recorded and that data will also be stored on university site. Service Use and Time and Travel Health Economics Questionnaires Minor updates to provide clarity on time frame of questions. RBQ-2 Teacher Version Inclusion of missing answer box. Follow-up demographics from Baseline demographics form has been shortened to create follow-up form so that families don't have to recomplete information that is only relevant at baseline at weeks 24 and 52.
SA3	REC Approval 26 April 2019	The study protocol has been amended with the following updates: 1. Update key trial contacts and include author list. 2. Change to safety reporting to only collect SAEs (i.e. not all adverse events), following consultation with the TSC. 3. Inclusion of reporting ESI (for this parent/carer group intervention and in this patient population, these are thought to be more relevant than collecting adverse events), following consultation with the TSC. 4. Clarity on inclusion/exclusion criteria (change to section A17-1 of IRAS form). 5. Withdrawals – clarity on when a participant is classed as enrolled and will be replaced. 6. Update to refer to measures as approved in previous amendments (e.g. VABS-3 not VABS-2, and demographics follow-up measure). 7. Inclusion of CGI-I score inter-rate reliability check. 8. Inclusion of fidelity checking for LAA (control) group as well as the URB group. 9. Inclusion of identifying participants through PICs as approved in previous amendment. 10. Clarity on protocol deviations. 11. Clarity on randomisation system design – the protocol originally stated that the first 10% of participants (25) would be randomly allocated. However, this 10% random element is actually incorporated for every randomisation throughout the trial to avoid predictability (i.e. there is a 10% chance at each randomisation that the preferred allocation will not be followed). Protocol section 7.3 has been updated to reflect this. Updated study documentation: Information for referrers document has been updated with amended eligibility criteria. EoI (mail out) cover letter has been amended to make as parent/carer friendly as possible, following PPI input Notice of Amendment IRAS Version 5.11 5 246595/1315218/13/10/90780. New study documentation: a poster to advertise the study to potential participants has been developed.
SA4	REC Approval 25 June 2019	Protocol updated to increase age range to 9 years and 11 months. New study document: parent EoI reminder form Change to IRAS A29: inviting families to participant using ASD-UK database.
SA5	REC Approval 9 July 2020	Update to target situation interview questionnaire.
SA6	REC Approval 5 May 2021	Update to the protocol to include the following changes: 1. Minor wording – typos, contact details, abbreviations. 2. Removal of ADOS contribution to CGI-I – primary outcome. 3. Introduction of focus group analysis for the impact of COVID-19 on group leaders, parents/carer and RAs. 4. Clarification of measurement of target vignette. 5. Flexibility of collection of data due to COVID-19 added to schedule of events. 6. Inclusion of impact of COVID-19 and edits to statistical analysis section.

PPI, patient and public involvement.

Sources of bias

There was no source of bias within this trial in relation to study design or recruitment of participants.

End of trial

The definition of end of trial was at the completion of the participant's last follow-up visit at 52 weeks.

Chapter 3 Coronavirus disease 2019

The COVID-19 pandemic has been an unprecedented event within this century and has had a significant effect on every clinical trial running during this time. Many trials halted recruitment, stopped delivering interventions or closed down. This was due to the impact of the pandemic and concomitant restrictions and redeployment of clinical staff leading to loss of capacity and necessary resource. In addition, staff sickness and participants unwilling to take part due to the risk of catching COVID-19 created additional challenges.

On 23 March 2020, the UK entered a strict lockdown, which included the enforcement of rules relating to leaving your property, which was only permitted for specific reasons and for restricted time periods. At this point, URB was still in the recruitment phase. As well as recruiting to the study, the URB and LAA intervention groups were running in person, mainly on clinical premises, facilitated by clinical personnel. Several decisions had to be made as to whether and how the trial could continue. These decisions included how to undertake informed consent with participants, how to deliver the interventions and how to manage follow-up assessments. NCTU worked closely with the TMG and sponsor to discuss each element of the trial and how to develop methods of ensuring its continuation. The development of methods to enable continuation was further complicated by local variations in how different sponsors at the three trial sites interpreted and enforced government guidelines.

With agreement from sponsor (CNTW), REC and the TSC, including patient and public involvement (PPI) members, the following activities were delivered remotely or via online secure platforms to ensure that the trial could continue:

Consent

Verbal/e-mail consent became the primary method for participants to provide consent. The PIS was read out to the participants in full over the telephone and e-mailed where possible. A consent proforma was then completed, ensuring that each point matched the approved consent form, to document that the participant agreed to each point.

This consent process was found to be both acceptable and feasible to potential participants – a total of 62 participants were consented using this method. Consent was briefly paused while these measures were developed, approved and put in place. Unfortunately, permission was not gained to reopen recruitment in Scotland, leading to the Lothian recruitment site closing permanently in March 2020. The closure of the Lothian recruitment site necessitated an increase in target recruitment at the remaining two research sites in order to achieve the required sample size. It also led to a requirement that additional groups were then run at the two remaining sites to accommodate the additional participants recruited at each site.

The delivery of the Understanding Repetitive Behaviours and Learning About Autism parent groups

A significant challenge following the onset of the COVID-19 restrictions was to determine how the interventions could be delivered via remote methods. Many factors had to be taken into consideration such as data protection for the participants and therapists, the use or potential limited use of technology and any associated costs and whether delivering groups online would be feasible for both staff to deliver and parents/carer to attend and could be delivered with fidelity. As both interventions had been designed to be delivered in a face-to-face format, the programmes had to be reviewed to ensure that the activities could be delivered in an online format and some adjustments needed to be made to the materials. At the time of lockdown, one group in CNTW was midway through delivery; the delivery of the group was paused while appropriate adjustments were made to the materials and the final four sessions of the group were then delivered to participants using an online format.

After March 2020 all LAA and URB groups were conducted entirely online using a range of free platforms; Microsoft Teams and Attend Anywhere. The platform adopted differed across NHS trusts based on local policies/guidance. The

use of online platforms to deliver the LAA and URB groups presented some challenges for group leaders. The majority of group leaders had not delivered therapeutic groups or teaching/training online previously and were therefore unfamiliar with the online platforms. Additional time was required at the start of each session to support parent/carers to access the online platform and some parents/carers required individual support with technology between sessions. Earlier versions of the online platforms had limited features, for example only four people were visible at once on screen and parent/carers were not visible at all while the group leader was displaying session slides. This meant that group leaders may have missed nonverbal cues that a parent/carer wished to contribute to a discussion or was finding the content of a session difficult. Similarly, managing group dynamics (e.g. dominating personalities) was potentially more difficult online. Due to COVID-19 restrictions many children did not attend school during lockdowns, this meant parents/carers' attention was often divided during the group sessions.

The move to online delivery of groups also brought some positives for parents/carers. Once initial technological challenges were overcome, some parents/carers reported that it was easier for them to attend the groups online as this greatly reduced the time commitment required as they did not need to travel to/from the group or organise child care. Parents/carers were also able to share visually with the group any environmental factors and strategies utilised within the home (e.g. social stories and visual timetables).

Baseline and follow-up assessments

After March 2020 the majority of baseline and follow-up assessments at weeks 10, 24 and 52 were conducted by telephone by the RAs. It was agreed that these assessments could take place over multiple sessions within a given time period to allow for more complete data collection and to reduce pressure on the participants to be available for a lengthy phone call, particularly as in many instances their children were not attending school due to the lockdown and therefore there was an increase in their parental duties at this time. In exceptional cases, and during periods of lockdown easing, as a reasonable adjustment some home visits were made to participants to undertake assessments if the participant was not able to participate comfortably by telephone. These visits were undertaken with the relevant social distancing requirements and following approval of the necessary risk assessments by senior research staff.

Fidelity assessments were also completed remotely due to COVID-19 restrictions. This involved the fidelity raters, who were located in Tyne & Wear (CNTW), reviewing a sample of LAA and URB session recordings via a virtual private network at Edinburgh University (Lothian NHS) or via Egress NHS encryption service (TEWV). While it was possible to complete the fidelity ratings remotely this method proved to be costly timewise due to ongoing server issues and difficulties streaming the videos.

Impact on the primary outcome

After reviewing all the baseline and outcomes measures, it was confirmed that all measures could be conducted over the telephone, with the exception of the ADOS-2 assessment. This measure, which is an observational play-based assessment with the child, is designed to be conducted face to face. Data from this measure were originally planned to be gathered at baseline and contribute to the CGI-I to provide raters with some detailed clinical insight into the child's level of ability and autistic traits. It was not planned that the measure would be repeated at follow-ups. From March 2020 onwards, ADOS-2 assessments were not undertaken with children due to the implementation of national governments' and NHS COVID-19 restrictions. Consequently, ADOS-2 scores were only obtained for two-thirds of the participants (155/227) and may therefore not be clinically representative of the full sample. Given this, the ADOS-2 scores were not included in the CGI-I analysis.

Impact on secondary outcomes

While it was determined that, with the exception of the ADOS-2, all other assessments could be collected remotely, the pandemic may have had an additional impact on responses to some or all of these other measures. During the

pandemic, schools were closed for considerable amounts of time and when they were in session they were subject to changes to procedures. These school-based changes may have impacted on teaching staff responses on the RBQ Teacher version; most particularly, they may have spent far less time with the children they were reporting upon than would have previously been the case. In addition, the changes to everyday life that were a consequence of restrictions may have impacted on children's RRB directly, for example the setting for the RRB may have no longer been somewhere that was accessed during lockdown (e.g. school, shopping centres or playgroups); indeed, a small number of scenarios identified during the TBVS were no longer relevant.

Restricted and repetitive behaviours were also assessed more generally using the RBQ-2, which requires parents/carers to rate their child's engagement in a range of RRB. It is difficult to determine the full impact of COVID-19 on the families who were part of the study. Many parents/carers reported changes in their child's well-being as a consequence of the pandemic; for some these changes may have been negative with their autistic child feeling anxious about how the pandemic would unfold and upset about disruptions to their routine, for others the changes may have been more positive with the child benefiting from a less demanding lifestyle with the focus on staying at home with family. For many families it may have been a combination of the two at different times. These circumstances therefore may have impacted in unanticipated ways on the behaviours captured by the RBQ-2.

In addition, for parents/carers the closure of schools and services meant that they often lost their expected everyday support networks and often became full-time caregivers of their autistic child. Recent research indicates that some autistic children experienced worsening in behavioural, social and developmental domains during the pandemic, while others thrived in a more restricted environment.

It is difficult to pinpoint what impact COVID-19 may have had on the sensitivity of our outcomes measures and the study is not powered to provide a definitive answer to these questions.

Impact on economic outcomes

In addition to the clinical effectiveness measures, there is a possibility that COVID-19 had an impact on the economic conclusions. With regard to the effectiveness measures, the impacts that have been noted for the primary and secondary outcomes will have also affected the economic evaluation when comparing the costs and the benefits. In addition, with regard to the measurement of resources used, the impacts of COVID-19 meant that there may have been less availability or willingness to access services as a result of lockdown measures. As such there may have been less services utilised by participants. However, given the unprecedented and stressful nature of the restrictions, the opposite may also be true if children needed greater support during this time. What should be noted is that whatever the effect may have been on resources, it would have likely had the same impact on both arms of the evaluation, in an equal manner, and therefore we would not expect to see significant differences between the arms.

Statistical considerations

Future practice

One unanticipated benefit of the COVID-19 pandemic was the opportunity to deliver the assessments and interventions via remote means. Our fidelity analysis, which included ratings of sessions delivered in the original face-to-face and remote formats, indicates that both methods of delivery are feasible, can be done with fidelity to the manual and are acceptable to parents/carers. Indeed, informal feedback from parents/carers during COVID-19 suggests that they were appreciative of the efforts of the research and clinical teams to continue with the study during a time when many clinical, educational and support services were closed. As such, we do now have some evidence that both URB and LAA are feasible and acceptable to delivery via remote methods. This has significant implications for the implementation of the programmes via clinical services to families who may struggle to attend the groups in a face-to-face format. A separately funded qualitative study is currently evaluating the findings of a series of focus groups undertaken following the completion of the main trial to investigate the impact of COVID-19 on delivery of the interventions.

Chapter 4 Results

Trial results

Participants were recruited to the study from NHS services in Northern England and Scotland. The first participant for the URB trial was randomised on 13 November 2018. The final participant was randomised on 15 September 2020. An internal pilot phase was conducted for 9 months after the commencement of recruitment (halfway through the planned 18-month recruitment phase). See figure 1 for recruitment progress. Due to the COVID-19 pandemic, several changes had to be made to the trial to ensure that recruitment and delivery of the interventions could continue. Recruitment was extended from 30 January 2020 to 31 May 2020 to allow as many participants to be consented as possible within the time frame. A further costed extension of 8 months was granted in November 2021 to allow for as much follow-up data to be collected as possible. The amended trial end date was 31 March 2022.

Potential participants were identified through the three clinical research sites, as well as through PICs. Clinicians were provided with information on the URB study and asked to introduce the study to families. This may have been in person at a clinic appointment, in a community setting/school, via telephone or by letter/e-mail. Clinicians gave potential families copies of the information sheets and an EoI form to be returned by the clinician or the family to the research team using the stamped addressed envelope provided. Families were also invited to take part through research databases such as ASD-UK. The local CRN at each site assisted with recruitment.

In total, 1829 potential participants were invited to participate into the trial. Please see figure 2 for CONSORT flow chart. Of these, 1563 declined and of these 422 potential participants reported their reasons for declining; 105 were not interested after further discussion, 41 did not consent and 14 were deemed not eligible. The main reasons for potential participants not being interested in the trial were due to other commitments such as child care, lack of time, financial issues and travel arrangements. These in combination accounted for 69 of the potential participants who declined. A further 11 potential participants did not consent following further information due to these factors. Other reasons recorded included concerns with a child participating in the study, no defined RRBs, child not living with the parent and a translator needed. There were several other factors that only affected one or two potential participants. Regarding the four participants deemed ineligible, this was due to the age range falling outside of the prespecified window.

Of those who were eligible, 227 were randomised. Of these, 113 were randomised to LAA and 114 were randomised to URB. As a consequence of missing data, 155 families have usable data at 24 weeks for the primary end point (see *Appendix 2*, *Table 24*).

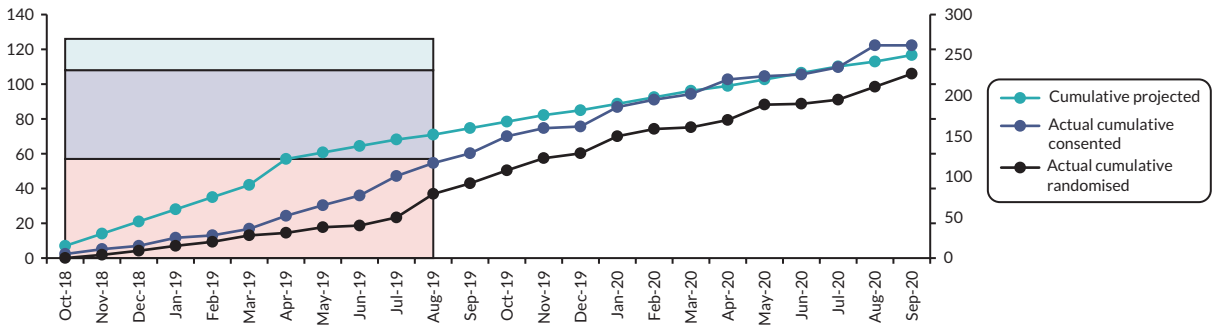

FIGURE 1 Recruitment showing actual consented, randomised and projected participants for the overall trial alongside the pilot trial which was given the green light in August 2019 to progress through to the main trial. Due to COVID-19 restrictions, Lothian stopped recruitment in March 2020.

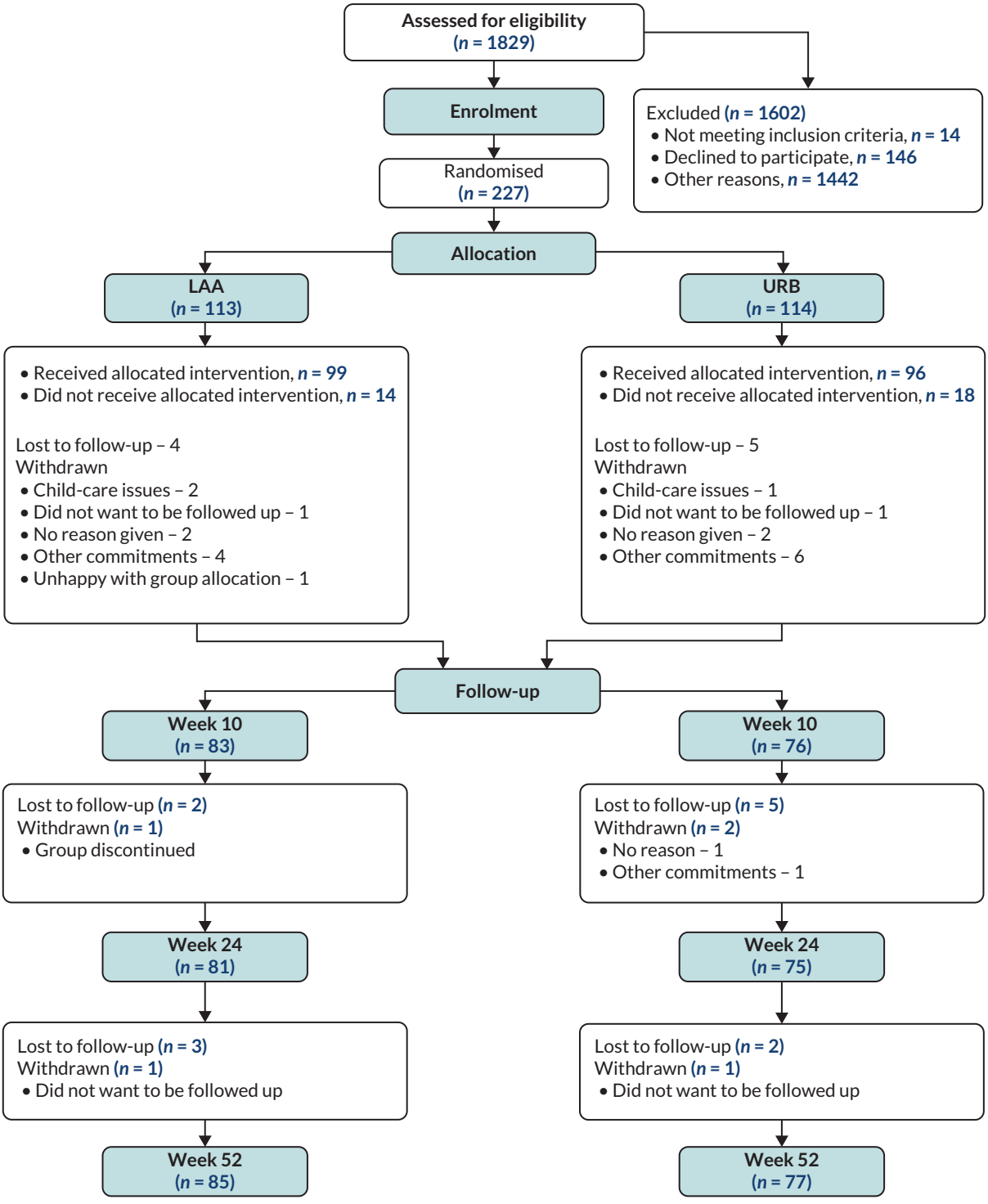

FIGURE 2 The CONSORT diagram and the recruitment and retention to the trial. Reproduced from Grahame *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4 0/. The figure includes minor additions and formatting changes to the original text.

Baseline data

Child characteristics

The summary of demographic variables used in the minimisation scheme for the randomised families (total = 227) are as follows:

The majority of children were from white ethnic backgrounds (85.9% vs. 14.1%). A breakdown of ethnicity by treatment arms showed that there were 85.84% in the LAA arm and 85.96% in the URB arm from white ethnic backgrounds. The largest age category was 3–5 years old (47.58%) whereas the smallest age category was 8–9 years (15.42%). Similarly, in both arms the majority were from the 3–5 years old age category (LAA, 46.9%; URB, 48.25%), whereas there were 16.81% in the LAA arm and 14.04% in the URB arm from the 8–9 years old category. In terms of gender, there were more males (79.74%) than females (20.26%) in the data set (males; LAA, 80.53%, URB, 78.95%). The families in the two trial arms were balanced on the variables (child's ethnicity, age and gender) that were used in the minimisation scheme.

A summary of all the baseline measures at child level are provided in *Table 4*, including descriptive statistics on categorical demographic variables and baseline child scores.

Table 4 shows that children from a white ethnic background are in the majority. Six children had missing information on ethnicity (three in each trial arm) and four children (two in each arm) were unclassified. The mean baseline age in the LAA arm was 6.23 years while the mean age in the URB arm was 6.16 with variability slightly higher in the former than the latter. The values of the mean total scores for SRS-2 and VABS-3 were similar in both trial arms.

From March 2020 onwards, ADOS-2 assessments were not able to be undertaken with children once NHS COVID-19 restrictions were implemented. ADOS-2 scores were only obtained for two-thirds of the participants (155/227) and may therefore not be clinically representative of the full sample. The ADOS-2 scores are presented in the appendix (see *Appendix 1*, *Table 23*). The values of SRS-2 scores, 83.9 and 82.83 in the LAA and URB, arms respectively, are interpreted as severe and strongly associated with clinical diagnosis of autism (see *Baseline characterisation and outcome measures*).

The values of VABS-3 ABC scores were 67.4 and 67.85 in the LAA and URB arms, respectively, and fall within the low range of adaptive functioning, indicating difficulties with adaptive behaviour/daily living skills that are consistent with a clinical sample of autistic children. For comparison to a wider sample, based on standardisation data, a mean score of 63.3 was reported for autistic children aged 3–8 with a concurrent intellectual disability and a mean score of 76.8 was reported for autistic children aged 3–8 without a concurrent intellectual disability. The range of scores reported for the SRS-2 (57–90) and the VABS-3 ABC (42–111) suggests a sample of autistic children with mixed abilities, including children with and without a concurrent intellectual disability.

Furthermore, *Table 4* presents the summary of the RBQ-2 baseline. In all baseline measures both trial arms were balanced in terms of available scores and the number of missing scores was similar in both trial arms. All comparisons here are exploratory with no formal statistical test. In general, the missing data pattern is similar in both trial arms.

Household and baseline characteristics of parent/carer

Table 5 shows the summary of child's household relations and the distribution of the baseline characteristics of the parent/carer. Data related to the child's other parent's baseline characteristics (where applicable) can be found in *Appendix 1*, *Table 22*. Consistent with the child-level data, the majority of parents/carers were white. Most of the parents/carers were married. Summary of baseline parent/carer scores and details about educational qualifications and jobs of the parents/carers are also reported. Trial arms were almost balanced across all measures.

Sample size available for analysis at primary end point

As a consequence of missing data required to calculate CGI-I scores (primary outcome) (see *Missing data*), usable data for the primary outcome analysis at the primary end point (24 weeks) was available from 155 families. Given that the target sample size was for 250 families providing data for analysis (125 per arm), the study collected less than the expected data at the primary end point. The implications of this are noted in the analysis of the primary outcome (see *Power consideration*). All outcomes are summarised and analysed according to the ITT principle on the basis of the number of randomised families to trial arms. All families included in the analyses received the treatment that they were randomised to.

TABLE 4 Baseline child characteristics

Variable	LAA			URB			Total		
	N[a] (missing)	Mean (SD)	Range	*N* (missing)	Mean (SD)	Range	*N* (missing)	Mean (SD)	Range
Age									
	113 (0)	6.23 (1.74)	3.25–9.83	114 (0)	6.16 (1.66)	3.03–9.96	227 (0)	6.2 (1.7)	3.03-9.96
Gender *n*/*N* (%)									
Female	22/113 (19.47%)			24/114 (21.05%)			46/227 (20.26%)		
Male	91/113 (80.53%)			90/114 (78.95%)			181/227 (79.74%)		
Missing	0/113 (0%)			0/114 (0%)			0/227 (0%)		
Child ethnicity *n*/*N* (%)									
Any white background	94/110 (85.45%)			94/111 (84.68%)			188/221 (85.07%)		
White and Black Caribbean	0/110 (0%)			0/111 (0%)			0/221 (0%)		
White and Black African	3/110 (2.73%)			0/111 (0%)			3/221 (1.36%)		
White and Asian	1/110 (0.91%)			1/111 (0.9%)			2/221 (0.9%)		
Any other mixed background	2/110 (1.82%)			2/111 (1.8%)			4/221 (1.81%)		
Indian	0/110 (0%)			0/111 (0%)			0/221 (0%)		
Pakistani	2/110 (1.82%)			2/111 (1.8%)			4/221 (1.81%)		
Bangladeshi	1/110 (0.91%)			2/111 (1.8%)			3/221 (1.36%)		
Any other Asian background	1/110 (0.91%)			1/111 (0.9%)			2/221 (0.9%)		
Caribbean	0/110 (0%)			0/111 (0%)			0/221 (0%)		
African	3/110 (2.73%)			6/111 (5.41%)			9/221 (4.07%)		
Any other African background	1/110 (0.91%)			1/111 (0.9%)			2/221 (0.9%)		
Chinese	0/110 (0%)			0/111 (0%)			0/221 (0%)		
Any other ethnic group	2/110 (1.82%)			2/111 (1.8%)			4/221 (1.81%)		
Missing	3/113 (2.65%)			3/114 (2.63%)			6/227 (2.64%)		

continued

TABLE 4 Baseline child characteristics (*continued*)

Variable	LAA			URB			Total		
	N[a] (missing)	Mean (SD)	Range	*N* (missing)	Mean (SD)	Range	*N* (missing)	Mean (SD)	Range
SRS-2									
	101 (12)	83.9 (7.96)	57–90	102 (12)	82.83 (7.71)	57–90	203 (24)	83.36 (7.83)	57–90
RBQ-2 Mean Total score									
	109 (4)	2.15 (0.33)	1.3–2.9	109 (5)	2.09 (0.35)	1.35–2.9	218 (9)	2.12 (0.34)	1.3–2.9
RBQ-2 Motor Sensory Behaviour									
	110 (3)	2.16 (0.43)	1.25–3	109 (5)	2.06 (0.44)	1.25–3	219 (8)	2.11 (0.44)	1.25–3
RBQ-2 Insistence on Sameness									
	109 (4)	2.1 (0.44)	1–3	110 (4)	2.09 (0.43)	1.33–3	219 (8)	2.1 (0.43)	1–3
RBQ Teacher Mean Total score									
	63 (50)	1.8 (0.41)	1–2.75	68 (46)	1.69 (0.33)	1.05–2.55	131 (96)	1.74 (0.37)	1–2.75
VABS-3 Communication									
	106 (7)	66.82 (18.51)	32–135	105 (9)	66.78 (15.38)	32–121	211 (16)	66.8 (16.98)	32–135
VABS-3 Socialisation									
	100 (13)	66.87 (9.17)	47–90	104 (10)	68.49 (8.95)	47–91	204 (23)	67.7 (9.07)	47–91
VABS-3 Daily Living Skills									
	106 (7)	70.53 (14.03)	32–115	103 (11)	71.36 (11.34)	48–106	209 (18)	70.94 (12.75)	32–115
VABS-3 ABC Score									
	97 (16)	67.4 (9.99)	42–111	98 (16)	67.85 (8.47)	51–96	195 (32)	67.63 (9.24)	42–111

a *N* is the number of available data.

TABLE 5 Household composition and baseline characteristics of parent/carer[a]

Variable	LAA *n*/*N* (%)	URB *n*/*N* (%)	Total *n*/*N* (%)
Household and family composition-relation			
Having both birth parents or any of adoptive mother/adoptive father/stepmother/stepfather/mother's partner/father's partner	77/111 (69.37%)	82/110 (74.55%)	159/221 (71.95%)
Having any of mother/father/adoptive mother/adoptive father/stepmother/stepfather/mother's partner/father's partner	107/111 (96.40%)	10/110 (99.09%)	216/221 (97.74%)
Having any of mother/father/adoptive mother/adoptive father/stepmother/stepfather/mother's partner/father's partner with child having at least one same-sex sibling of any type[b]	51/111 (45.95%)	46/110 (41.82%)	97/221 (43.89%)
Having any of mother/father/adoptive mother/adoptive father/stepmother/stepfather/mother's partner/father's partner with child having no same-sex sibling of any type,[a] this includes having no siblings	56/111 (50.45%)	63/110 (57.27%)	119/221 (53.85%)
Missing	2/113 (1.77%)	4/114 (3.51%)	6/227 (2.64%)
Parent ethnicity[a]			
Any white background	98/110 (89.09%)	94/110 (85.45%)	192/220 (87.27%)
African	7/110 (6.36%)	6/110 (5.45%)	13/220 (5.91%)
Asian (Indian, Pakistani, Bangladeshi, any other Asian)	4/110 (3.64%)	6/110 (5.45%)	10/220 (4.55%)
Any other ethnic group	2/110 (1.82%)	4/110 (3.64%)	6/220 (2.73%)
Missing	3/113 (2.65%)	4/114 (3.51%)	7/227 (3.08%)
Parental marital status[a]			
Single	24/111 (21.62%)	22/109 (20.18%)	46/220 (20.91%)
Married and civil partnered	67/111 (60.36%)	64/109 (58.72%)	131/220 (59.55%)
Separated/divorced	4/111 (3.6%)	8/109 (7.34%)	12/220 (5.45%)
Other	16/111 (14.41%)	15/109 (13.76%)	31/220 (14.09%)
Missing	2/113 (1.77%)	5/114 (4.39%)	7/227 (3.08%)

continued

TABLE 5 Household composition and baseline characteristics of parent/carer[a] (*continued*)

Variable	LAA	URB	Total
	n/*N* (%)	*n*/*N* (%)	*n*/*N* (%)
Parent profession[a]			
Professional occupations	28/110 (25.45%)	25/108 (23.15%)	53/218 (24.31%)
Administrative and secretarial occupations	13/110 (11.82%)	4/108 (3.7%)	17/218 (7.8%)
Personal service occupations	9/110 (8.18%)	19/108 (17.59%)	28/218 (12.84%)
Sales and customer service occupations	4/110 (3.64%)	9/108 (8.33%)	13/218 (5.96%)
Process, plant and machine operatives	1/110 (0.91%)	1/108 (0.93%)	2/218 (0.92%)
Elementary occupations	5/110 (4.55%)	4/108 (3.7%)	9/218 (4.13%)
Full-time parent (never worked)	33/110 (30%)	33/108 (30.56%)	66/218 (30.28%)
Full-time student	3/110 (2.73%)	2/108 (1.85%)	5/218 (2.29%)
Unemployed	7/110 (6.36%)	6/108 (5.56%)	13/218 (5.96%)
Retired	0/110 (0%)	1/108 (0.93%)	1/218 (0.46%)
Other	5/110 (4.55%)	4/108 (3.7%)	9/218 (4.13%)
Missing	5/113 (4.42%)	6/114 (5.26%)	11/227 (4.85%)
Parent educational qualifications			
None	5/111 (4.5%)	5/110 (4.55%)	10/221 (4.52%)
1–4 passes at CSE, GCSE, O level	6/111 (5.41%)	4/110 (3.64%)	10/221 (4.52%)
5 or more passes at CSE, GCSE, O level	11/111 (9.91%)	18/110 (16.36%)	29/221 (13.12%)
A levels or equivalent	36/111 (32.43%)	31/110 (28.18%)	67/221 (30.32%)
Postgraduate degree	50/111 (45.05%)	51/110 (46.36%)	101/221 (45.7%)
Missing	5/113 (4.42%)	5/114 (4.39%)	10/227 (4.41%)

Variable	*N*[a] (missing)	Mean (SD)	Range	*N*[a] (missing)	Mean (SD)	Range	*N*[a] (missing)	Mean (SD)	Range
PSE									
	96 (17)	3.22 (0.85)	0.4–4.75	91 (23)	3.06 (0.91)	1–5	187 (40)	3.14 (0.88)	0.4–5
APSI total									
	104 (9)	23.79 (9.05)	8–55	107 (7)	23.71 (10.38)	6–58	211 (16)	23.75 (9.72)	6–58
APSI comorbid physical symptoms									
	103 (10)	5.83 (3.5)	0–20	106 (8)	6.13 (4.08)	0–20	209 (18)	5.99 (3.8)	0–20
APSI core deficits									
	107 (6)	10.26 (4.53)	2–25	106 (8)	10.49 (4.99)	0–25	213 (14)	10.38 (4.75)	0–25
APSI comorbid behavioural symptoms									
	101 (12)	7.67 (4.03)	0–18	104 (10)	7.11 (3.89)	1–20	205 (22)	7.39 (3.96)	0–20
WEMWBS									
	108 (5)	43.61 (8.31)	15–62	107 (7)	45.21 (8.57)	27–67	215 (12)	44.41 (8.46)	15–67
AFEQ total									
	103 (10)	141.69 (15.14)	107–173.62	106 (8)	140.9 (18.01)	98.04–184	209 (18)	141.29 (16.62)	98.04–184
AFEQ experience being parent									
	106 (7)	35.9 (7.29)	14–53	105 (9)	35.46 (7.61)	16.35–52	211 (16)	35.68 (7.43)	14–53
AFEQ family life									
	107 (6)	27.18 (5.07)	13–39	107 (7)	26 (6.36)	12–40	214 (13)	26.59 (5.77)	12–40
AFEQ child development understanding social relationships									
	103 (10)	43.68 (7.43)	19.33–59	107 (7)	43.86 (8.07)	23–67	210 (17)	43.78 (7.75)	19.33–67
AFEQ child symptoms									
	104 (9)	35.2 (4.08)	26.62–48.62	106 (8)	35.32 (4.15)	27–48.15	210 (17)	35.26 (4.11)	26.62–48.62

PSE, parent/carer self-efficacy.
a Parent/carer defined as parent/carer who attended the intervention and completed the necessary assessments.
b *N* is the number of available data. Any type of siblings is sister/brother/stepsister/stepbrother/half-sister/half-brother.
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Attendance and fidelity of delivery of both intervention arms (Learning About Autism and Understanding Repetitive Behaviours)

Attendance at parent group sessions

A summary of attendance at parent group sessions showed that the average number of sessions attended in LAA and URB arms was five out of eight, according to the data provided by the sites.

Clinical Global Impression – Improvement scale inter-rater reliability

For 10% of the sample, the CGI-I were independently rated by a second trained researcher. Fleiss' Kappa and Cohen's Kappa were used to assess inter-rater reliability.

Fleiss' Kappa as an index of inter-rater agreement between two raters was calculated and presented in *Table 6*. The agreement between raters was moderate by this measure (0.495) and significantly different from zero ($p < 0.001$). In addition, Cohen's Kappa showed the agreement between raters was substantial (0.692) and significantly different from zero ($p = 0.01$). The conclusion from the two measures indicated that there was agreement between the two raters. This gives us confidence in the CGI-I ratings used in the primary analysis.

Fidelity of therapists' delivery of Learning About Autism and Understanding Repetitive Behaviours intervention sessions

Analysis of fidelity of therapists' delivery of the intervention to the manual was undertaken for both arms on 10% of randomly selected session recordings assessed by four independent raters. Sessions were selected for rating from face-to-face delivery (pre-COVID-19 restrictions) and online delivery (LAA: 8 face-to-face and 7 remote vs. URB: 9 face-to-face and 6 remote). For both arms the fidelity of delivery of the intervention was excellent: the LAA group overall percentage agreement between the independent raters was 93.6% ($\kappa = 0.846$), 92.7% for delivery ($\kappa = 0.897$) and 94.5% for content. For the URB group overall percentage agreement was 94.9% ($\kappa = 0.91$), 97.2% for delivery ($\kappa = 0.963$) and 90.1% for content.

Outcomes of serious adverse events and events of special interests

Among a total of five SAEs, two were hospital admissions due to appendix pain and mouth pain for the child (both in LAA) and one was hospital admission due to COVID-19 for parent/carer (in URB). The two other SAEs were a reported discharge from the hospital after having a heart attack for parent/carer (in URB) and one was a reported meningitis for the child (in URB). More details are reported in *Appendix 2*, *Table 25*.

Table 7 presents 24 ESI (see *Chapter 2*). Of these, 9 were reported within the LAA arm and 15 within the URB arm. The largest number of ESI were reported during the intervention phase of the URB arm (9/24) while six ESI were reported in each treatment arm during the follow-up phase of the study. Parental stress and school difficulties were the most frequently reported ESI across trial arms and three ESI were linked to COVID-19.

Among 24 ESI, at the end of the study 14 were reported as still ongoing, 1 was resolved which was in the URB arm and the status for 9 was unknown.

Among a total of 14 ongoing ESI across 3 sites, 10 were reported in CNTW and 4 in TEWV. The only one resolved ESI was located in CNTW and ESIs with unknown status were equally distributed across sites.

TABLE 6 Summary of inter-rater reliability analysis on rating CGI-I

Inter-rater reliability measure	No. of subjects	Value	*p*-value
Fleiss' Kappa for two raters	16	0.495	< 0.001
Cohen's Kappa for two raters (weights: squared)	16	0.692	0.01

TABLE 7 Events of special interest

ESI category	LAA *N*		URB *N*	
Study phase	**During intervention**	**During follow-up phase**	**During intervention**	**During follow-up phase**
Moved out of area			1	
School difficulties		1	1	2
Financial difficulties	1			
Parental stress	2	2	2	
Physical health (child)			1	
Physical health (parent)		1	1	
Mental health (sibling)			1	
Caring responsibilities (grandparent)		1	1	
Family bereavement			1	2
COVID-19 physical health (family)				1
COVID -19 financial difficulties		1		
COVID -19 family separation				1
Total per study phase	**3**	**6**	**9**	**6**
Overall total	**9**		**15**	

Primary analysis

Power consideration

There were a total of 72/227 (31.72%) data missing at the primary end point. A blinded sample size re-estimation indicated that a minimum of 179 families were needed to retain 80% power and by 224 families, 90% power is achievable. Therefore, in terms of the number of families that were randomised (227), the study has a minimum of 90% power. In terms of actual data available at 24 weeks for the primary end point, a post hoc power calculation based on 155 (227–72 = 155) families contributing to the primary end point at 24 weeks resulted in 70–75% power. This means that with the available data at 24 weeks, the trial collected fewer than the expected data and so is unable to answer, with any certainty, whether or not the URB intervention is statistically more effective compared with the LAA intervention.

Comparing improvement between trial arms according to Clinical Global Impression – Improvement scale at 24 weeks

In this section, the primary analysis is presented – *Table 8* shows the estimate of OR, which is the ratio between the odds of improvement in the two arms (URB/LAA). Primary analysis was adjusted for the effects of gender, ethnicity and age.

The result shows that the odds of improvement on average was 39% higher in the URB arm compared to the LAA arm [OR 1.39, 95% confidence interval (CI) 0.52 to 3.69; $p = 0.51$]. However, the result is not statistically significant and the CI is sufficiently wide enough to contain differences favouring either URB or LAA. The primary analysis represented by risk difference is provided in *Appendix 3*.

TABLE 8 Summary of analysis on CGI-I

	LAA	URB	URB vs. LAA	
CGI-I	***n/N* (%)**	***n/N* (%)**	**Odds ratio (95% CI)**	***p*-value[a]**
Improved	10/81 (12.35%)	11/74 (14.86%)	1.39 (0.52 to 3.69)	0.51
Not improved	71/81 (87.65%)	63/74 (85.14%)		

CI, confidence interval.
a *p*-value obtained from GEE with binomial distribution.

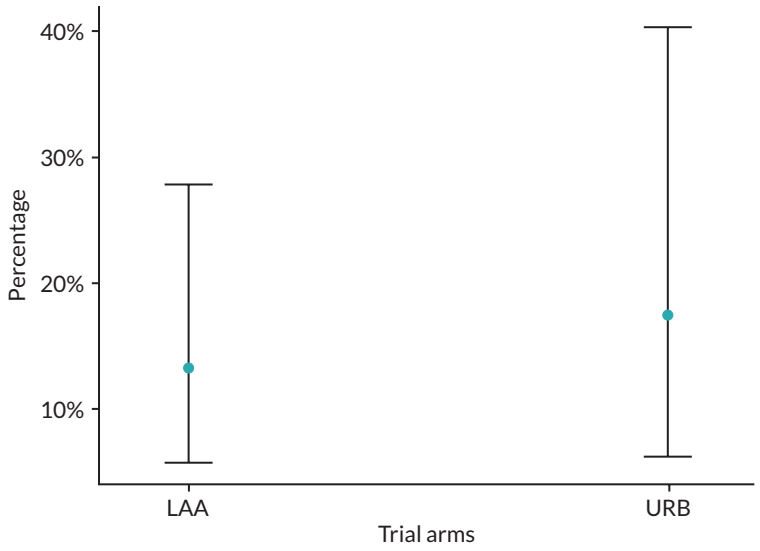

FIGURE 3 Predicted probabilities of improvement in trial arms.

As expected from the analysis, *Figure 3* shows the mean probability of improvement in URB and the LAA arms. As noted in *Table 8*, there is no evidence of any difference between trial arms.

The percentages of (non-)improvement according to CGI-I within the levels of gender, age and ethnicity per trial arms and in the entire sample are presented in *Appendix 2*, *Figures 14–16*.

Prespecified secondary analysis

Analyses of target behaviour vignette, improvement and impact on families

Each family provided two separate TBVs at baseline, which were then captured again at follow-up. An expert panel rated the follow-up vignettes in relation to change compared to baseline on a nine-point scale from 'very much improved' to 'disastrously worse' in relation to the behaviour reported and the impact on the family unit. Ratings of three or less (very much improved, markedly improved, definitely improved) were used to determine a positive response and this was used to define a 'responder', and binary variables (responder vs. non-responder) were calculated for the analysis (see *Chapter 2*, *Secondary child outcome measure*).

TVB change scores (behaviour and impact, responder vs. non-responder) were compared across the arms at each time point in vignette change scores overall.

Table 9 shows the results of the analysis of change in the TBV at 10, 24 and 52 weeks. Under 'Positive response in behaviour improvement', the odds of improvement on average were 92% higher in the URB arm compared to the LAA arm (OR 1.92, 95% CI 1.10 to 3.39; p = 0.02) at 24 weeks (primary end point). Unlike the primary analysis shown in *Table 8*, this result is statistically significant. Similarly, for 'Positive response in impact on family', the URB arm included significantly more responders than the LAA arm at 24 weeks (OR 2.10, 95% CI 1.14 to 3.92; p = 0.02).

Comparison of the change scores on the TBV between trial arms at 10 weeks shows that in the URB arm the participants were more likely to have a 'Positive response in behaviour improvement' and 'Positive response in impact on family' compared with the LAA arm. It is noteworthy that there was no evidence of any differences between the trial arms at 52 weeks for all the TBV measures.

Secondary analysis on continuous outcomes

Differences between and within treatment arms in secondary outcomes

From *Table 10*, it can be seen that there are few statistically significant differences between the URB and LAA arms in relation to changes in the child secondary outcomes. A significant difference is found between the URB arm and the LAA on the RBQ-2 Motor Sensory Behaviour subscale score at 10 weeks compared to baseline. However, it is noteworthy that in the LAA arm, the RBQ-2 Motor Sensory Behaviour score on average increased significantly at 10 weeks compared to baseline (+0.09, 95% CI 0.03 to 0.16), which may account for this difference between the arms.

For RBQ Teacher Mean Total score, a significant difference is also noted between the arms at 52 weeks compared to baseline. However, this is most likely accounted for by a decrease in the LAA arm at 52 weeks compared baseline.

Turning to the parent-reported measures, the parent/carer self-efficacy (PSE) score changed significantly at 10 weeks compared to baseline (+0.34, 95% CI 0.09 to 0.6) comparing URB with LAA with evidence of more parental self-efficacy in the URB arm compared with the LAA arm.

There were no other between arm differences at any time point on any of the secondary outcomes.

Changes over time within both arms can be seen in relation to the VABS-3 subscales at 24 weeks indicating some improvement in adaptive functions for children in both arms. It is important to note that, although these changes are statistically significant, they are small and do not represent a clinically meaningful change in adaptive function.

Changes are also apparent in a number of parent measures (PSE, APSI and WEMWBS) and family functioning measured by the AFEQ. The results indicate that parents in both trial arms may have benefited from the interventions they received. These changes are largely maintained to 52 weeks.

Missing data

Summary of missing data

Table 11 indicated that there was a total of 72 (31%) missing data sets in primary outcome with higher rate in the URB arm (14% vs. 18%). The highest rate of missing data in primary outcome was from the Lothian site (43%). Thirty-seven per cent of data were missing pre lockdown versus 19% post lockdown. There was no evidence that these were different (p = 0.21) using a logistic regression model.

TABLE 9 Analysis of the TBV

Variable	LAA *n/N* (%)[a]	URB *n/N* (%)[a]	Total *n/N* (%)[a]	URB vs. LAA: odds ratio (95% CI)	*p*-value[b]
Positive response in behaviour improvement					
10 weeks	17/151 (11.26%)	40/136 (29.41%)	57/287 (19.86%)	3.26 (1.76 to 6.26)	**0.00**
24 weeks	28/148 (18.92%)	40/132 (30.3%)	68/280 (24.29%)	1.92 (1.1 to 3.39)	**0.02**
52 weeks	31/150 (20.67%)	38/135 (28.15%)	69/285 (24.21%)	1.52 (0.88 to 2.64)	0.14
Positive response in impact on family					
10 weeks	14/151 (9.27%)	27/136 (19.85%)	41/287 (14.29%)	2.4 (1.21 to 4.94)	**0.01**
24 weeks	21/148 (14.19%)	33/132 (25%)	54/280 (19.29%)	2.1 (1.14 to 3.92)	**0.02**
52 weeks	27/150 (18%)	29/135 (21.48%)	56/285 (19.65%)	1.23 (0.68 to 2.22)	0.49

a *n* is number of responders and *N* is number of available data.
b *p*-values are obtained from logistic regression model.

Note
p-value for significant effects are in bold.

TABLE 10 Secondary analysis on continuous outcomes

	LAA			URB			Total	
Variable/time point	*N*	Mean (SD)	Change from baseline diff (95% CI)	*N*	Mean (SD)	Change from baseline diff (95% CI)	*N*	URB-LAA: change from baseline diff (95% CI)
RBQ-2 Sensory Motor Behaviour; lower score is lower levels of RRB								
Baseline	110	2.16 (0.43)		109	2.06 (0.44)		219	
10 weeks	83	2.19 (0.43)	**0.09 (0.03 to 0.16)**	76	2.05 (0.45)	−0.01 (−0.09 to 0.07)	159	**−0.10 (−0.21 to 0)**
24 weeks	81	2.13 (0.44)	0.04 (−0.02 to 0.11)	73	2.04 (0.42)	0 (−0.08 to 0.08)	154	−0.04 (−0.14 to 0.07)
52 weeks	83	2.1 (0.46)	−0.02 (−0.09 to 0.04)	75	2.04 (0.47)	−0.01 (−0.09 to 0.07)	158	0.01 (−0.09 to 0.11)
RBQ-2 Insistence on Sameness; lower score is lower levels of RRB								
Baseline	109	2.1 (0.44)		110	2.09 (0.43)		219	
10 weeks	82	2.16 (0.44)	**0.07 (0 to 0.13)**	76	2.13 (0.44)	0.04 (−0.04 to 0.12)	158	−0.03 (−0.13 to 0.07)
24 weeks	80	2.13 (0.41)	0.03 (−0.03 to 0.1)	72	2.09 (0.45)	−0.01 (−0.09 to 0.07)	152	−0.05 (−0.15 to 0.06)
52 weeks	83	2.17 (0.46)	0.05 (−0.02 to 0.12)	75	2.19 (0.43)	**0.07 (0 to 0.15)**	158	0.02 (−0.08 to 0.12)
RBQ-2 Mean Total score; lower score is lower levels of RRB								
Baseline	109	2.15 (0.33)		109	2.09 (0.35)		218	
10 weeks	83	2.19 (0.36)	**0.08 (0.03 to 0.12)**	75	2.12 (0.34)	0.02 (−0.04 to 0.08)	158	−0.06 (−0.13 to 0.02)
24 weeks	80	2.15 (0.35)	0.04 (−0.01 to 0.09)	72	2.1 (0.35)	0.01 (−0.05 to 0.07)	152	−0.03 (−0.11 to 0.04)
52 weeks	83	2.16 (0.38)	0.02 (−0.03 to 0.07)	75	2.14 (0.36)	0.03 (−0.02 to 0.09)	158	0.01 (−0.06 to 0.09)
RBQ Teacher Mean Total score; lower score is lower levels of RRB								
Baseline	63	1.8 (0.41)		68	1.69 (0.33)		131	
10 weeks	51	1.79 (0.41)	−0.02 (−0.1 to 0.06)	43	1.7 (0.37)	0.05 (−0.05 to 0.14)	94	0.07 (−0.06 to 0.19)
24 weeks	52	1.76 (0.36)	−0.04 (−0.13 to 0.04)	38	1.72 (0.33)	0.03 (−0.07 to 0.12)	90	0.07 (−0.06 to 0.19)
52 weeks	46	1.65 (0.35)	**−0.17 (−0.26 to −0.09)**	37	1.7 (0.42)	0.02 (−0.08 to 0.12)	83	**0.18 (0.05 to 0.31)**

continued

TABLE 10 Secondary analysis on continuous outcomes (*continued*)

	LAA			URB			Total	
Variable/time point	*N*	Mean (SD)	Change from baseline diff (95% CI)	*N*	Mean (SD)	Change from baseline diff (95% CI)	*N*	URB-LAA: change from baseline diff (95% CI)
VABS-3 Communication; higher score indicates a higher level of ability								
Baseline	106	66.82 (18.51)		105	66.78 (15.38)		211	
24 weeks	79	69.16 (18.02)	**2.52 (1 to 4.04)**	72	69.51 (15.81)	1.61 (−0.17 to 3.42)	151	−0.94 (−3.26 to 1.4)
VABS-3 Daily Living Skills; higher score indicates a higher level of ability								
Baseline	100	66.87 (9.17)		104	68.49 (8.95)		204	
24 weeks	79	69.72 (9.73)	**1.99 (0.66 to 3.36)**	69	70.17 (10.13)	**1.66 (0.19 to 3.14)**	148	−0.32 (−2.32 to 1.65)
VABS-3 Socialisation; higher score indicates a higher level of ability								
Baseline	106	70.53 (14.03)		103	71.36 (11.34)		209	
24 weeks	80	72.89 (14.76)	**2.12 (0.78 to 3.47)**	71	74.68 (11.99)	**2.43 (0.73 to 4.16)**	151	0.21 (−1.94 to 2.37)
VABS-3 ABC; higher score indicates a higher level of ability								
Baseline	97	67.4 (9.99)		98	67.85 (8.47)		195	
24 weeks	77	70.04 (12.26)	**1.83 (0.96 to 2.7)**	66	70.41 (10.24)	**2.09 (0.87 to 3.32)**	143	0.2 (−1.28 to 1.68)
PSE; higher score is more parent self-efficacy								
Baseline	96	3.22 (0.85)		91	3.06 (0.91)		187	
10 weeks	74	3.36 (0.76)	0.16 (−0.01 to 0.33)	65	3.57 (0.68)	**0.51 (0.31 to 0.7)**	139	**0.34 (0.09 to 0.6)**
24 weeks	75	3.5 (0.75)	**0.3 (0.13 to 0.47)**	63	3.46 (0.72)	**0.42 (0.22 to 0.61)**	138	0.11 (−0.14 to 0.37)
52 weeks	73	3.73 (0.58)	**0.49 (0.32 to 0.67)**	68	3.74 (0.67)	**0.69 (0.5 to 0.88)**	141	0.19 (−0.07 to 0.44)
APSI Total; higher score represents more parenting stress								
Baseline	104	23.79 (9.05)		107	23.71 (10.38)		211	
10 weeks	81	22.2 (8.61)	−1.44 (−3.22 to 0.34)	75	20.17 (7.78)	**−3.41 (−5 to −1.82)**	156	−1.97 (−4.36 to 0.43)

Variable/time point	LAA			URB			Total	
	N	Mean (SD)	Change from baseline diff (95% CI)	*N*	Mean (SD)	Change from baseline diff (95% CI)	*N*	URB-LAA: change from baseline diff (95% CI)
24 weeks	79	20.49 (9.16)	**−2.79 (−4.6 to −1.01)**	71	20.45 (8.62)	**−2.85 (−4.48 to −1.23)**	150	−0.11 (−2.53 to 2.32)
52 weeks	81	19.42 (8.9)	**−3.7 (−5.49 to −1.93)**	75	18.89 (7.11)	**−4.46 (−6.05 to −2.86)**	156	−0.81 (−3.2 to 1.59)
WEMWBS; higher score is favourable								
Baseline	108	43.61 (8.31)		107	45.21 (8.57)		215	
24 weeks	79	45.04 (8.08)	1 (−0.47 to 2.48)	71	46.6 (8.58)	0.92 (−0.69 to 2.54)	150	−0.13 (−2.3 to 2.05)
52 weeks	81	46.83 (8.05)	**2.93 (1.47 to 4.4)**	74	47.13 (7.92)	**1.67 (0.08 to 3.28)**	155	−1.3 (−3.45 to 0.86)
AFEQ Total; lower score is favourable								
Baseline	103	141.69 (15.14)		106	140.9 (18.01)		209	
24 weeks	79	137.06 (15.57)	**−4.28 (−6.92 to −1.65)**	69	134.19 (15.69)	**−5.28 (−8.13 to −2.46)**	148	−1.04 (−4.9 to 2.8)
52 weeks	81	133.19 (16.77)	**−8.27 (−10.89 to −5.66)**	75	132.28 (16.99)	**−7.92 (−10.69 to −5.18)**	156	0.34 (−3.45 to 4.12)
AFEQ Experience being parent; lower score is favourable								
Baseline	106	35.9 (7.29)		105	35.46 (7.61)		211	
24 weeks	79	32.89 (7.21)	**−2.79 (−4.22 to −1.38)**	69	32.26 (7.53)	**−2.54 (−3.92 to −1.19)**	148	0.2 (−1.78 to 2.17)
52 weeks	79	32.47 (7.31)	**−3.22 (−4.64 to −1.8)**	75	31.27 (7.58)	**−3.68 (−5.02 to −2.36)**	154	−0.49 (−2.44 to 1.45)
AFEQ Family life; lower score is favourable								
Baseline	107	27.18 (5.07)		107	26 (6.36)		214	
24 weeks	79	25.99 (5.16)	−0.85 (−1.75 to 0.04)	70	24.12 (5.59)	**−1.68 (−2.75 to −0.62)**	149	−0.82 (−2.2 to 0.55)
52 weeks	81	24.98 (5.46)	**−1.86 (−2.75 to −0.98)**	75	24.27 (5.73)	**−1.91 (−2.94 to −0.86)**	156	−0.04 (−1.39 to 1.32)

continued

TABLE 10 Secondary analysis on continuous outcomes (*continued*)

	LAA			URB			Total	
Variable/time point	***N***	**Mean (SD)**	**Change from baseline diff (95% CI)**	***N***	**Mean (SD)**	**Change from baseline diff (95% CI)**	***N***	**URB-LAA: change from baseline diff (95% CI)**
AFEQ Child development understanding social relationships; lower score is favourable								
Baseline	103	43.68 (7.43)		107	43.86 (8.07)		210	
24 weeks	79	42.75 (7.74)	−1.07 (−2.23 to 0.08)	69	42.17 (7.33)	**−1.69 (−2.96 to −0.42)**	148	−0.63 (−2.34 to 1.07)
52 weeks	81	41.14 (7.54)	**−2.57 (−3.72 to −1.43)**	75	41.52 (7.67)	**−2.4 (−3.63 to −1.16)**	156	0.17 (−1.5 to 1.85)
AFEQ Child symptoms; lower score is favourable								
Baseline	104	35.2 (4.08)		106	35.32 (4.15)		210	
24 weeks	79	35.42 (3.97)	0.29 (−0.47 to 1.05)	70	35.76 (3.83)	0.57 (−0.3 to 1.42)	149	0.3 (−0.84 to 1.44)
52 weeks	80	34.64 (4.08)	−0.64 (−1.39 to 0.11)	75	35.23 (3.75)	0.08 (−0.78 to 0.91)	155	0.74 (−0.39 to 1.86)

LAA, URB: RBQ-2, VABS-3, CI, confidence interval; PSE, parent/carer self-efficacy, APSI, WEMWBS, AFEQ.

TABLE 11 Missing rates in CGI-I

Variable	LAA *n/N* (%)	URB *n/N* (%)	Total *n/N* (%)
Missing rate in CGI-I			
	32/227 (14.1%)	40/227 (17.62%)	72/227 (31.72%)
Missing rate in CGI-I per site			
CNTW	14/56 (25%)	17/58 (29.31%)	31/114 (27.19%)
Edinburgh and Lothians	11/29 (37.93%)	13/27 (48.15%)	24/56 (42.86%)
TEWV	7/28 (25%)	10/29 (34.48%)	17/57 (29.82%)
Missing rate in CGI-I pre and post lockdown[a]			
Pre lockdown	28/158 (17.72%)	31/158 (19.62%)	59/158 (37.34%)
Post lockdown	4/69 (5.8%)	9/69 (13.04%)	13/69 (18.84%)

a Note that the date of week 24 visits when CGI-I is missing is not available (it is missing too); thus randomisation dates are compared with lockdown date.

Weighted generalised estimating equation for Clinical Global Impression – Improvement scale

As noted in the methodology section, we used WGEE to explore the impact of missing data on the primary outcome. *Table 12* contains the result of WGEE on the primary outcome. There was no evidence of a difference between arms but the CI surrounding the odds of improvement was sufficiently wide enough to include important differences favouring either arm.

Completion, lost to follow-up and withdrawal

Eleven participants did not attend any parent group and therefore did not contribute to the primary outcome. In addition, two participants (0 in LAA and two in URB) withdrew but it was possible to use their data for CGI-I ratings. It did not appear that there was any difference between groups in this respect, but there did appear to be more withdrawals in the URB arm compared with the LAA arm (*Table 13*).

TABLE 12 Weighted GEE analysis for CGI-I

	LAA *n/N* (%)	URB *n/N* (%)	Total *n/N* (%)	URB vs. LAA after applying WGEE Odds ratio (95% CI)	*p*-value
Missing rate	32/113 (28.32%)	40/114 (35.09%)	72/227 (31.72%)	1.38 (0.49 to 3.87)	0.54

TABLE 13 Completion, withdrawals and lost to follow-up

Variable	LAA *n/N* (%)	URB *n/N* (%)	Total *n/N* (%)
Completed	85/113 (75.22%)	78/114 (68.42%)	163/227 (71.81%)
Lost to follow-up	15/113 (13.16 %)	16/114 (14.04%)	31/227 (14.54%)
Withdrawn	13/113 (11.5%)	20/114 (17.7%)	33/227 (13.66%)

Chapter 5 Economic evaluation

Introduction

An economic evaluation has been described as a comparative analysis of alternative courses of action in terms of both their costs and consequences.[44] The economic evaluation for this study is detailed within the Health Economics Analysis Plan. In the URB trial, three economic evaluations were undertaken: a cost-effectiveness analysis (CEA), a cost–utility analysis (CUA) and a cost-consequence analysis (CCA). The economic evaluations were carried out from an NHS and patient perspective over the time horizon of one year.

A CEA equates an intervention's extra cost to its extra effectiveness when measured using a natural or clinical outcome. For this CEA, the clinical outcome was the proportion of children who met the target difference in the CGI-I at 24 weeks – the primary outcome URB trial (see *Chapter 2*). The primary outcome of the CEA was incremental (i.e. the extra cost) per additional person meeting the target difference in the CGI-I at 24 weeks.

In addition to the CEA, a CUA was undertaken, in which the costs were compared to a measure that combines quantity and quality of life – in this instance quality-adjusted life-years (QALYs). The primary outcome of the CUA was the incremental cost per QALY at 52 weeks from the perspective of the caregiver and the child using the EQ-5D-5L health-related quality-of-life instrument.[45] A secondary outcome measure for the CUA was the incremental cost per QALY gained at 52 weeks from the perspective of the child using the Child Health Unity 9D (CHU-9D) completed by a proxy quality-of-life instrument.[46,47]

The final form of economic evaluation undertaken was a CCA. Using this approach, the costs are compared to the outcomes from the trial using a balance sheet approach. The outcomes for the CCA are the primary and secondary outcomes that were collected as part of the URB trial.[48] These measures are described in detail in *Chapter 2* and their results are presented in *Chapter 4*. The purpose of the CCA is twofold. First, it provides additional context that can help understand what might drive the results seen in the CEA and the CUA. Second, both the CEA and CUA have a comparatively narrow consideration of what constitutes a benefit (or harm) of the intervention (e.g. the single measure of clinical effectiveness for the CEA and health-related quality of life for the CUA). Thus, both the CEA and CUA may not include some impacts that stakeholders may find important when making a decision about whether or not URB should be used in preference to LAA.

Methods

The economic evaluation was carried out using the NICE guidelines for health technology assessment that were applicable when the analysis of the URB data began.[49] The version of this guidance has since been updated.[50]

Data collection

Intervention costs

The cost of the URB intervention was estimated from trial data and clinical expert opinion from the trial team. The URB group is delivered by two community-based professionals (facilitators) who have experience working with children with ASD and this was felt to be reflective of how the intervention would be delivered in routine practice. Professional time (the facilitators) required for this intervention was estimated using the clinical expertise of the trial team who designed the intervention. The amount of time and the type of staff required for group facilitations were estimated from expert opinion from the trial team who designed the intervention. Facilitator costs were derived by estimating the time required to prepare and run the group multiplied by the hourly rate for the facilitator based on published estimates.[51] Printed materials costs were assumed based on trial teams' estimates of printing rates.

For the LAA arm, the sessions were two hours long and were also delivered by a group facilitator trained and approved by the NAS. The NAS staff rates, the time required to run the group and the printed material costs were all provided by correspondence from the NAS.[52]

For both the URB and LAA arms, a per participant cost was derived by dividing the total intervention cost by the average number of participants per group. The number of participants per group was based upon an assumption of nine per group which was the most common group size in the Northumberland, Tyne and Wear NHS Foundation Trust which was the site that ran the most groups.

Each randomised participant was allocated a treatment cost based upon which arm they were randomised to. The intervention costs are summarised in *Appendix 5*, *Table 30*.

Service utilisation costs

To measure the services utilised by participants throughout the course of the trial, a Service Use Questionnaire (SUQ) was administered to participants. The SUQ asked participants how many times in the last 6 months they had accessed health services. The SUQ was administered at baseline, 24 weeks and 52 weeks follow-up. The SUQ included the number of hospital appointments, inpatient hospital stays (including reason and duration) and the type and number of healthcare appointments. Appointments differentiated between the different places where appointments were held, for example the participants' home; by phone/virtually and within the practice. The SUQ also asked participants to record the medications that they were taking, the duration they had been taking them for and the dose of the medication.

Costs for hospital outpatient appointments, day cases and inpatient stays were obtained from published NHS reference costs.[53] Medication costs were estimated from the British National Formulary (BNF);[54] the access dates can be seen in *Appendix 5*, *Table 37*.

Costs for community-based appointments such as GP or distract nurse appointments were costed using the Unit Costs of Health and Social Care.[51] Hospital inpatient unit costs were calculated by calculating the number of days that the participant had an inpatient stay by the unit cost derived from NHS reference costs.[53] Day-case costs were multiplied by the number of days that the participant was in hospital for a day case. The unit costs used are detailed in *Appendix 5*, *Tables 33*, *34*, *36* and *37*. Medication costs were calculated by multiplying the unit costs of the correct dose of drug by the duration that the participant had been taking it (up to a maximum of 6 months to match the recall period of each administration of the SUQ).

A per participant cost for resource use was generated for each recall period at baseline, and for the 24 weeks and 52 weeks follow-up data collection points. This participant cost was inclusive of appointments, medications and hospital visits. Costs at 24 weeks and 52 weeks follow-up were summed so that an overall cost for each participant over the trial follow-up was estimated (note the costs at baseline were used as part of the 'adjusted analysis' as described below and described in *Appendix 5*, *Table 35*). Once costs for each participant were derived, then descriptive statistics such as a mean cost for each arm were generated along with suitable measures of variance, for example standard deviations.

Patient private care costs and time and travel costs

In the base-case analysis only NHS costs were included in the CEA and the CUA. However, to explore the impact of the costs borne by the participants in terms of privately paid for care and time and travel costs for accessing care were also included in a sensitivity analysis. This analysis assessed whether the inclusion of the patient costs affected the conclusions.

Participants were asked about any private costs they had incurred in managing their child's symptoms. This including asking about services such as homeopathy, traditional Chinese medicine or private counselling costs. The cost of such private care was an assumption based on estimates from private providers to provide the service. These estimates can be seen in *Appendix 5*, *Table 38*.

In order to help estimate the time and travel costs of accessing care, a time and travel questionnaire (TTQ) was administered at baseline. In this questionnaire, the participant detailed the journeys made to appointments in the community and the hospital. For journeys that were undertaken by public transportation or taxis, participants were asked to provide details about any fares that were paid. Any journeys that were undertaken by car were costed using the fuel rate based on the business and self-employed expenses rate per mile from the Travel Analysis Guidance.[55] In addition, any fees for car parking were also included in the journey costs. For hospital transport, costs were derived from the NHS reference costs 2019–20.[53]

In addition to travel costs, the costs for the participant's time were included both for time to travel to and attend community-based and hospital appointments and for the management of days that the child had taken out of school. Participants were asked if they had to take time away from their work, care or studies to look after a child during school hours. An estimate was used for the number of days that would be taken off school based on a study by Totsika *et al.*[56] This study assessed patterns of non-school attendance for those on the autism spectrum. They found a median absence of 2 days per 23 days. This was extrapolated over 6 months to give a total of 16 days per 6-month period. A school day was assumed to be 6 hours, and paid time was costed based on the Office for National Statistics (ONS) annual survey of hours and earnings (ASHE) average salary rate.[57] Unpaid time was costed at the leisure time rate based on the study by Verbooy *et al.*, estimate for hourly estimate value of leisure time and unpaid work.[58] The time the participants spent attending the hospital and outpatient appointments was reported in the TTQ for community and hospital-based appointments and costed at the ONS rate.

The cost for time and travel for each type of service contact was calculated by taking the mean from the time and travel costs in the sample. This was then multiplied by the number of the appointments for each trial participant for both the hospital and the community. This was added to the private costs to make up the time, travel and private costs for each participant. An average cost for each trial arm was then calculated. The time and travel costs are summarised in *Appendix 5*, *Table 31* and the school absence costs are summarised in *Appendix 5*, *Table 32*.

Estimation of effects

Clinical Global Impression – Improvement scale outcomes

The primary effectiveness outcome measure for the cost-effectiveness analysis is achieving at least the target difference in CGI-I at 24 weeks. The outcome is expressed as a percentage of children who achieved their targeted outcome. As noted above, the results for the CEA are expressed as the incremental cost per additional child reaching their target improvement in the CGI-I outcome.

Quality-adjusted life-year outcomes

The primary measure of effects for the CUA is the QALY derived from responses to the EQ-5D-5L (and CHU-9D in a secondary analysis). Participant related quality of life is measured at baseline, 24 and 52 weeks for both the EQ-5D-5L and CHU-9D. The EQ-5D-5L was completed by the child's primary caregiver as a measure of their own health-related quality of life. The CHU-9D is by a proxy on behalf of the child as a measure of their health-related quality of life.

There is a new UK value set for the EQ-5D-5L which could be used to derive utility values.[59] However, at present, this data set is still being validated and NICE advised mapping the values from the previous EQ-5D-3L data set, and as such, the results from the EQ-5D-5L were cross-walked to the EQ-5D-3L using the van Hout cross-walk,[60] the recommended method at the time the analysis was started.

As noted above, the primary outcome for the CUA was the incremental cost per QALY based on responses to the EQ-5D-5L. The likelihood that this value is below a given value for society's willingness to pay for a QALY (including NICEs threshold for a QALY gain of £20,000 and £30,000) was estimated.[50] A secondary outcome for the CUA was the incremental cost per QALY based on responses to the CHU-9D. The likelihood that this value is below a given value from a range of society's willingness-to-pay thresholds for a QALY was also estimated.

Balance sheet of outcomes

In addition to the CEA and the CUA economic evaluations, there was also to be a CCA, which lists the results of the primary and secondary trial outcomes alongside the costs for each arm. The list of the secondary outcomes in this trial are detailed in *Table 10* in *Chapter 4*.

Analysis of costs and benefits

Continuous and count variables are expressed with appropriate descriptive statistics. This includes means and standard deviations and, for difference in outcome measures, confidence intervals. The relationship between the costs and the outcomes was analysed using a seemingly unrelated regression (SUR). A SUR is a type of regression analysis which permits the simultaneous estimation of costs data and effects data, calculated at an individual level. In addition, the SUR controlled for additional covariates (such as age and gender) that may affect costs, effects or both.[61] The data were analysed in the Stata™ software program.[62]

The price year for costs and benefits was 2020 in Great British pounds (GBP). As the cost and benefits for this study were measured within 1 year, no discounting was applied aligning the NICE technology assessment guidelines.[49]

Missing data

For the complete case analysis, only those with complete case data were included. To be included in the complete case data set all relevant trial instruments had to be completed. This included both the visit and the service use questionnaire which had to be noted as complete on the visit record. In addition, to be considered completed the questionnaires must not have had large sections that were not completed (e.g. no values, positive or negative, were given in the entire section). For instruments used to derive (i.e. the EQ-5D-5L or CHU-9D) QALY values, data were missing if any one of the three time points of the baseline, 24 weeks or 52 weeks was not completed.

To account for those with missing data, multiple imputation was carried out. Costs and QALY were imputed using a chained imputation approach using paired mean matching approach using nearest neighbour. This approach was chosen because the data were missing at similar levels and costs and QALYs were considered to be interrelated variables.

In addition to the CEA and the CUA economic evaluations, there was also to be a CCA, which lists the results of the primary and secondary trial outcomes alongside the costs for each arm. The list of the secondary outcomes in this trial are detailed in *Table 7*.

Sensitivity analysis

Deterministic sensitivity analysis

Deterministic sensitivity analysis was carried out to assess the variability of different parameters on the outcomes of the economic evaluation. One of the key sensitivity analyses was to broaden the cost perspective to include the costs falling on participants and their families.

Stochastic sensitivity analysis

To assess the robustness of the study sampling, non-parametric bootstrapping was carried out to assess the uncertainty around the conclusions. Bootstrapping is a technique which resamples a single data set to create many simulated samples to assess statistical precision. In this case, this meant that the difference in net benefit was estimated for each simulated data set.

In this study, 1000 iterations of the bootstrapping procedure were performed. For the CUA, bootstrapping was carried out for the costs and both the QALY outcomes. The results of the bootstrapping URB were used to develop cost-effectiveness planes. For the CUA, the horizontal axis represents the difference in adult QALYs or child QALYs and the vertical axis represents the corresponding difference in costs.

For the CCA, appropriate measures of statistical variance, for example mean and standard deviation, were presented.

Coronavirus disease 2019

Due to the onset of the COVID-19 pandemic during this trial, the modality of the provision of the intervention changed from an in-person to an online format due to the constrictions around in-person meetings during the periods of lockdown. After a discussion with the trial team about how this would change the costs of the interventions, no important differences in costs could be identified for the different modes of delivery. The trial team used a free online platform, and the participants used their own electronic devices to participate. The clinical effectiveness analysis found that there was no evidence of a difference in the effectiveness in the interventions between modalities. As such, there was no specific sensitivity analysis for the impact of COVID-19 on the provision of interventions or its impact within the economic evaluation.

Reporting standard

The reporting of this economic evaluation was assessed against the consolidated health economic evaluation reporting standards (CHEERS checklist).[63] This checklist notes the items to include when reporting economic evaluations of health interventions, and it was completed to make sure all relevant information was reported.

Results

Response rates

The response rates for the SUQ and the TTQ and are summarised in *Table 14*.

As *Table 14* shows, response rates for the SUQ and TTQ at baseline were high but did drop for the SUQ at subsequent follow-up time points. There appears to be no obvious differences in the pattern of missing data between trial arms The response rates for the EQ-5D-5L and the CHU-9D are summarised in *Table 15*. The results for the missing data for the EQ-5D-5L and the CHU-9D follow a similar pattern to the cost questionnaires (see *Table 14*). The results for data completeness for the primary outcome (the CGI-I) completeness data are also summarised in *Table 15*.

Total resource use

The summary of the use of health services captured by the SUQ are shown in *Table 16*.

A number of different cost elements are important drivers of total cost. This includes children and young people's mental health services costs such as speech and language therapist costs and occupational therapy costs. *Table 16* summarises the costs at 24 and 52 weeks; costs were also calculated at baseline from the preceding 6 months of the trial. As described in the method, these costs were used to adjust for baseline costs in the SUR and are summarised in *Appendix 5*.

Health-related quality of life

The utility values from both the EQ-5D-5L and the CHU-9D health-related quality-of-life instruments are summarised in *Table 17*.

TABLE 14 Response rates of service use questionnaire and time and travel questionnaire

	LAA group (*n* = 113)			URB group (*n* = 114)		
	Data completeness (%)					
Questionnaire	Baseline	24 weeks	52 weeks	Baseline	24 weeks	52 weeks
SUQ	93% (*n* = 105)	70% (*n* = 79)	72% (*n* = 81)	94% (*n* = 107)	62% (*n* = 71)	65% (*n* = 74)
TTQ	79% (*n* = 89)			69 % (*n* = 79)		

TABLE 15 Data completeness of health-related quality-of-life questionnaires and completeness and improvement on the CGI-I scale

	LAA group (*n* = 113)			URB group (*n* = 114)		
	Data completeness (%)					
Outcome	**Baseline**	**24 weeks**	**52 weeks**	**Baseline**	**24 weeks**	**52 weeks**
CHU-9D	81% (*n* = 92)	66% (*n* = 75)	71% (*n* = 80)	82% (*n* = 93)	62% (*n* = 71)	63% (*n* = 72)
EQ-5D-5L	92% (*n* = 104)	70% (*n* = 79)	71% (*n* = 80)	89% (*n* = 102)	61% (*n* = 70)	66% (*n* = 75)
CGI-I completeness of data % (*n*)	71% (*n* = 81)			65% (*n* = 74)		
Significant improvement in CGI-I score from baseline % (*n* =)	12% (*n* = 10)			15% (*n* = 11)		

n, number.

TABLE 16 Appointment and drug costs in each arm

	LAA group			URB group		
	Appointments					
	Mean (£) (SD)			Mean (£) (SD)		
Cost category	24 weeks	52 weeks	Overall mean	24 weeks	52 weeks	Overall mean
GP	25 (37)	20 (42)	41 (64)	36 (56)	25 (46)	61 (87)
GP out of hours	6 (31)	6 (34)	14 (66)	1 (9)	2 (12)	3 (16)
Community nurse	2 (6)	2 (10)	3 (10)	1 (4)	11 (76)	13 (80)
Community support worker	1 (8)	7 (44)	9 (47)	3 (22)	2 (12)	6 (26)
Social worker	17 (55)	18 (56)	30 (101)	13 (53)	16 (60)	31 (95)
CAMHS worker	55 (191)	316 (2310)	406 (2571)	115 (515)	163 (529)	301 (1043)
School nurse	59 (285)	139 (1080)	221 (1333)	62 (468)	12 (34)	17 (47)
Counsellor	9 (66)	2 (15)	11 (82)	4 (35)	7 (46)	12 (60)
NHS 24/NHS 111 phone line	1 (3)	1 (4)	2 (4)	1 (2)	1 (4)	2 (5)
Psychiatrist	18 (127)	18 (97)	10 (60)	76 (350)	112 (405)	208 (708)
Psychologist	38 (102)	50 (140)	82 (178)	100 (231)	52 (161)	161 (350)
Occupational therapist	139 (471)	121 (383)	229 (578)	268 (633)	269 (852)	531 (1356)
Paediatrician	187 (291)	195 (288)	371 (440)	243 (412)	185 (399)	444 (772)
Speech and language therapist	259 (541)	217 (502)	448 (764)	213 (418)	408 (883)	629 (1137)
Accident and emergency	17 (48)	27 (63)	35 (85)	6 (26)	17 (72)	26 (93)
Other consultations						
Other	83 (278)	73 (198)	166 (377)	72 (227)	28 (84)	104 (256)
Medications						
Atomoxetine	2 (16)	2 (17)	2 (17)	0 (0)	0 (0)	0 (0)
Mirtazapine	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Propranolol	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Sertraline	0 (0)	0 (0)	0 (0)	0 (0)	0 (1)	0 (2)
Fluoxetine	0 (0)	0 (0)	0 (0)	1 (1)	0 (1)	0 (2)
Other medications						
Other	83 (199)	94 (202)	146 (350)	71 (186)	88 (262)	173 (410)

TABLE 17 Utility scores in the URB and LAA groups

	LAA group (*n* = 113)				URB group (*n* = 114)			
	Mean (SD)				Mean (SD)			
Outcome	Baseline	24 weeks	52 weeks	QALYs	Baseline	24 weeks	52 weeks	QALYs
CHU-9D	0.80 (0.11)	0.81 (0.11)	0.84 (0.10)		0.78 (0.11)	0.80 (0.10)	0.82 (0.11)	
Child's QALYs using CHU-9D (*n* = 121)				0.82 (0.08)		-		0.81 (0.08)
EQ-5D-5L	0.81 (0.19)	0.82 (0.21)	0.85 (0.17)		0.73 (0.23)	0.81 (0.21)	0.79 (0.21)	
Parents' QALYs using EQ-5D-5L (*n* = 130)				0.79 (0.18)				0.82 (0.16)

As *Table 17* shows, there is a small amount of additional QALYs based on responses to the EQ-5D-5L in the URB arm compared with the LAA arm. The CHU-9D-based QALYs are slightly higher on average for the LAA arm compared with the URB arm. It should be noted that in neither case should these differences be over-interpreted as there was no evidence of any difference in QALYs for either measure of QALYs; this table does not show the results of any statistical tests for a difference.

Economic evaluation

Cost-effectiveness analysis

The results of the CEA analysis are shown in *Table 18*. As this table shows, URB is on average more costly and more effective than LAA. The incremental cost per additional child achieving the target difference of over £35,000 for URB compared with LAA. This deterministic analysis however does not reflect the imprecision in estimates of cost or effects.

Complete case cost–utility analysis using quality-adjusted life-years based on responses to the EQ-5D-5L

The results of the complete CUA using QALYs based on responses to the EQ-5D-5L are shown in *Table 19*. The results are shown as a cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC). These are graphic ways of demonstrating the probability of the intervention's cost-effectiveness across a range of different values for society's willingness to pay for an outcome. The cost-effectiveness plane is in the form of a scatter plot (*Figure 4*) and CEAC with the points expressed on an *x* and *y* axis (*Figure 5*).

The results reported in *Table 19* for the complete case analysis show that the URB arm is on average more costly than the LAA arm. The CIs for the adjusted difference in costs have both positive and negative values, meaning that there is also a possibility that URB could be both more or indeed less costly compared with LAA. There is, on average, additional QALYs for URB compared with LAA. The CI however includes zero. Given the very small average increase in QALYs and more substantial increase in cost per patient on average for URB compared with LAA, the point estimate for the incremental cost per QALY gained for URB compared with LAA was almost £700,000. This estimate does not reflect the imprecision in estimates of costs of QALYs. To illustrate this, as described in the methods above, bootstrapping of incremental costs and QALYs was conducted, and these were used to plot how incremental costs and QALYs might vary (see *Figure 4*). As *Figure 4* shows, for the majority of plots (85%) URB is more costly. The estimates of QALYs are evenly distributed (for 53% of the bootstraps URB provides more QALYs). This imprecision is reflected in the cost-effectiveness acceptability curve that is graphically shown in *Figure 5* and in tabular form in the final four columns of *Table 19*. *Figure 5* and *Table 19* show that URB is unlikely to be considered cost-effective compared to LAA over all the threshold values for society's willingness to pay for an additional QALY.

Secondary and sensitivity analyses

Table 20 and *Figures 6* and *7* show the imputed sample for the EQ-5D-5L which is a broadly similar picture to the complete case analysis described above. With the larger sample available when data in imputed there is still a slightly larger additional effect on average but at a slightly lower additional average cost for the URB arm compared with the LAA arm. The incremental cost per QALY gained for this analysis is almost £45,000 and there is at best a fair chance that URB would be considered cost-effective over the range of threshold values for society's willingness to pay for a QALY.

Cost–utility analysis using the Child Health Unity 9D and complete case analysis

The results for the complete case CUA using the CHU-9D values for the QALYs are summarised in *Table 20* and *Figures 8* and *9*. The results show a very small effect in favour of URB with a larger cost differential compared with the EQ-5D-5L analysis reported above. Overall, the pattern of findings is the same and the URB intervention is unlikely to be considered cost-effective over a range of different willingness to pay for a QALY.

TABLE 18 Costs-effectiveness analysis of the children achieved target CGI-I

Data	Intervention	Cost (£) (CI)	ΔCost (£)	Children achieved target CGI-I	Δ Children achieved target CGI-I	ICER (ΔCost/ΔChildren achieved target) (£) CGI-I
Complete case data (*n* = 136)	LAA (*n* = 71)	£2655 (£1803 to £3507)		0.13		
	URB (*n* =65)	£3389 (£2359 to £4417)	£734	0.15	0.02	£36,700

Δ, difference; ICER, incremental cost-effectiveness ratio.

TABLE 19 Cost–utility analysis of the complete case data

Data	Intervention	Unadjusted cost (£) (CIs)	Adjusted ΔCost (£) (CIs)	Unadjusted QALY (EQ-5D-5L) (CIs)	Adjusted Δ QALY (EQ-5D-5L) (CIs)	ICER (ΔCost/ΔQALY) (EQ-5D-5L) (£)	Probability URB cost-effective at different threshold values for society's willingness to pay for a QALY			
							£0	£20,000	£30,000	£50,000
Complete case data (*n* = 129)	LAA (*n* = 68)	£2725 (1838 to 3611)		0.79 (0.74 to 0.83)			85%	78%	73%	67%
	URB (*n* = 61)	£3394 (2307 to 4480)	£685 (−525 to 1895)	0.83 (0.79 to 0.87)	0.001 (−0.04 to 0.043)	£685,000	15%	22%	27%	33%

Δ, difference; ICER, incremental cost-effectiveness ratio.

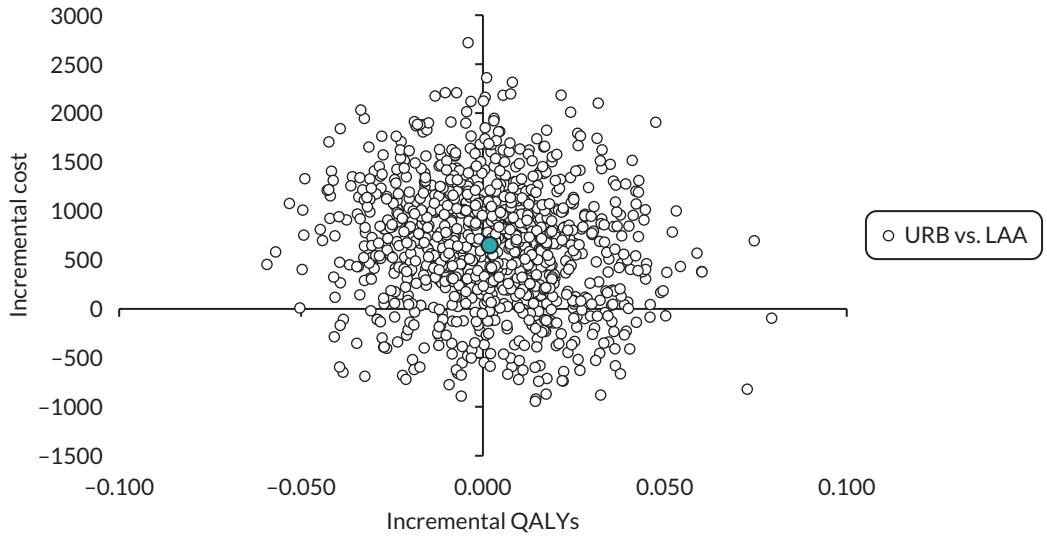

FIGURE 4 Cost-effectiveness plane for the complete data. Quality-adjusted life-years based on response to the EQ-5D-5L.

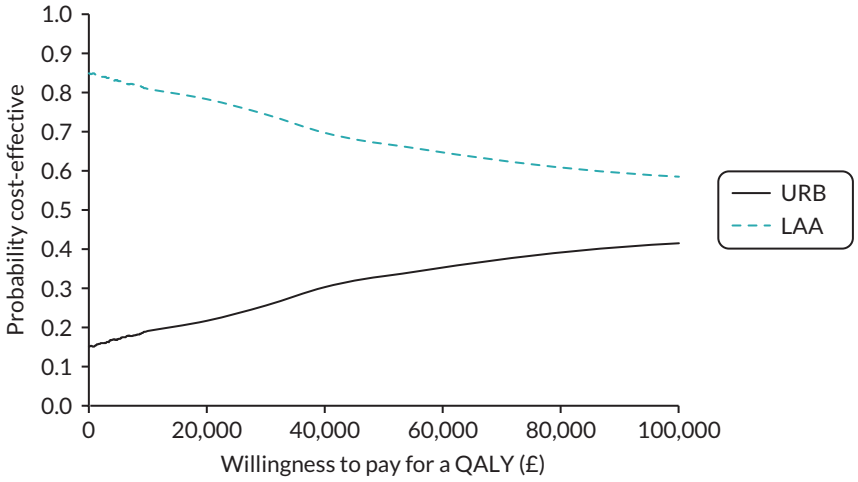

FIGURE 5 Cost-effectiveness acceptability curve for the complete case data. Quality-adjusted life-years based on response to the EQ-5D-5L.

Cost–utility analysis using the Child Health Unity 9D and imputed data

The results for the imputed CHU-9D sample are shown in *Table 20*, *Figures 10* and *11*. These data are broadly similar to those already presented. Although LAA is slightly more effective on average and has a lower cost on average, the likelihood of URB being cost-effective compared with LAA over the range of threshold values for society's willingness to pay is low.

Cost–utility analysis for the imputed case data for the EQ-5D-5L where patient costs are included

The results for this analysis are shown in in *Table 20*, *Figures 12* and *13*. The inclusion of the cost borne by the child and carers does not change the pattern of results already seen. Compared with LAA, URB is unlikely to be considered cost-effective over the range of threshold values for society's willingness to pay for a QALY.

TABLE 20 Cost–utility analysis for the secondary analyses and sensitivity analyses

Analysis	Data	Intervention	Unadjusted cost (£) (CIs)	Adjusted ΔCost (£) (CIs)	Unadjusted QALY (EQ-5D-5L) (CIs)	Adjusted ΔQALY (EQ-5D-5L) (CIs)	ICER (ΔCost/ΔQALY) (EQ-5D-5L) (£)	Probability URB is cost-effective at different threshold values for society's willingness to pay for a QALY			
								£0	£20,000	£30,000	£50,000
Cost–utility analysis of the imputed case data for the EQ-5D-5L	Imputed case data (*n* = 199)	LAA (*n* = 101)	£2644 (2028 to 3261)		0.78 (0.75 to 0.82)			84%	63%	56%	46%
		URB (*n* = 98)	£3005 (2287 to 3723)	£445 (−387 to 1278)	0.84 (0.79 to 0.87)	0.01 (−0.02 to 0.04)	£44,500	16%	37%	44%	54%
Cost–utility analysis using the CHU-9D	Complete case data (*n* = 120)	LAA (*n* = 62)	£2394 (1701 to 3087)		0.82 (0.80 to 0.84)			97%	93%	90%	85%
		URB (*n* = 58)	£3250 (2205 to 4440)	£922 (−1567 to 2001)	0.81 (0.79 to 0.83)	0.001 (−0.002 to 0.023)	£922,000	3%	7%	10%	15%
Cost–utility analysis of the imputed case data for the CHU-9D	Imputed case data (*n* = 181)	LAA (*n* = 90)	£2450 (1946 to 2954)		0.82 (0.80 to 0.83)	−0.005 (−0.022 to 0.012)	LAA is dominant	88%	90%	89%	87%
		URB (*n* = 91)	£2822 (2068 to 3576)	£444 (−265 to 1256)	0.80 (0.79 to 0.82)			12%	10%	11%	13%
Cost–utility analysis of the imputed case data for the EQ-5D-5L including time, travel and private costs	Imputed case time, travel and private data (*n* = 199)	LAA (*n* = 101)	£2934 (2290 to 3577)		0.78 (0.75 to 0.82)			89%	76%	68%	60%
		URB (*n* = 98)	£3367 (2609 to 4126)	£526 (−339 to 1392)	0.83 (0.80 to 0.86)	0.006 (−0.027 to 0.039)	£87,667	11%	24%	32%	40%

Δ, difference; ICER, incremental cost-effectiveness ratio.

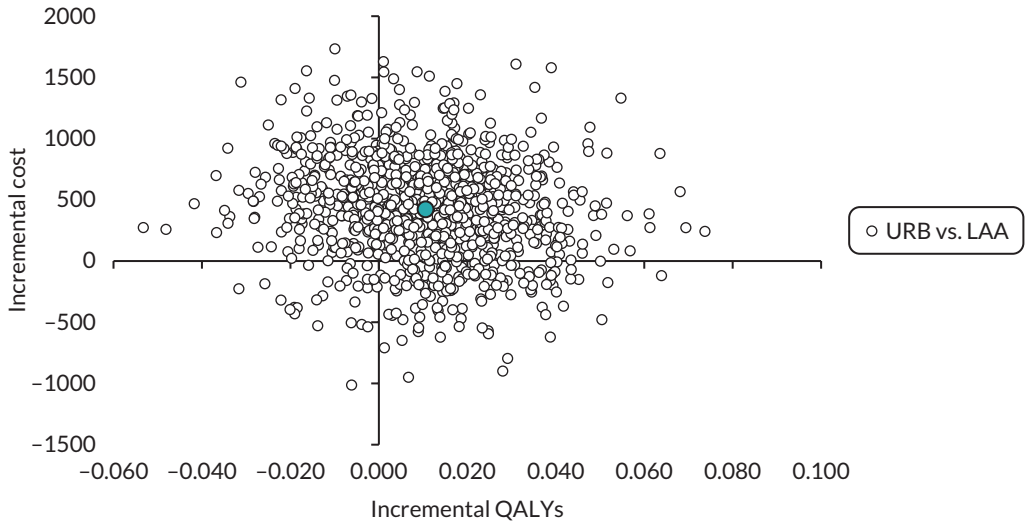

FIGURE 6 Costs-effectiveness plane for the imputed case data for the EQ-5D-5L.

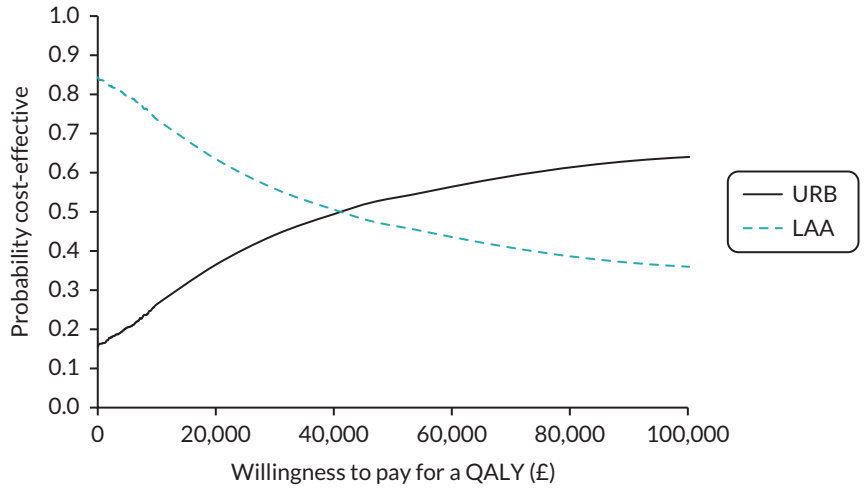

FIGURE 7 Cost-effectiveness acceptability curve for the imputed case data for the EQ-5D-5L.

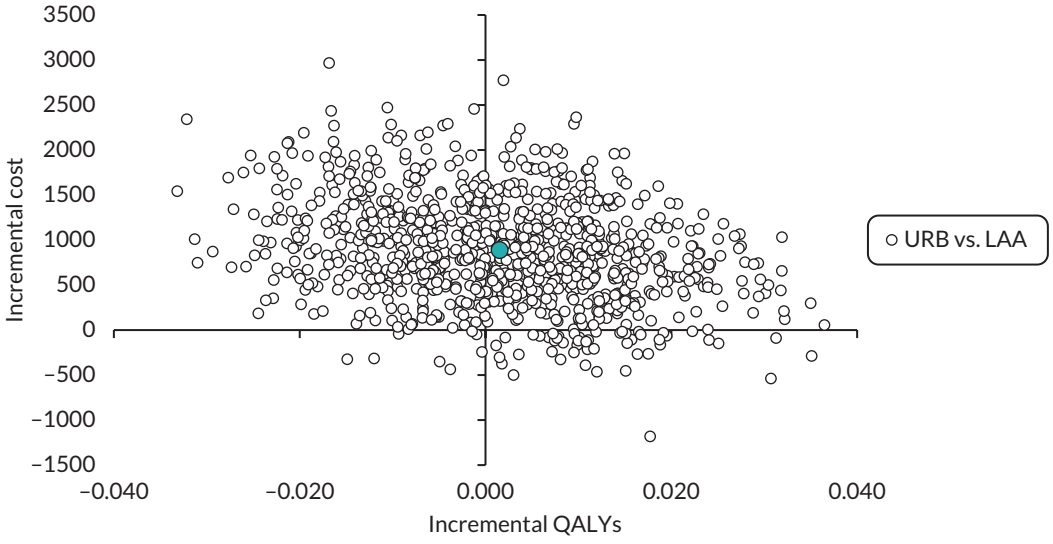

FIGURE 8 Costs-effectiveness plane for the complete case data for the CHU-9D.

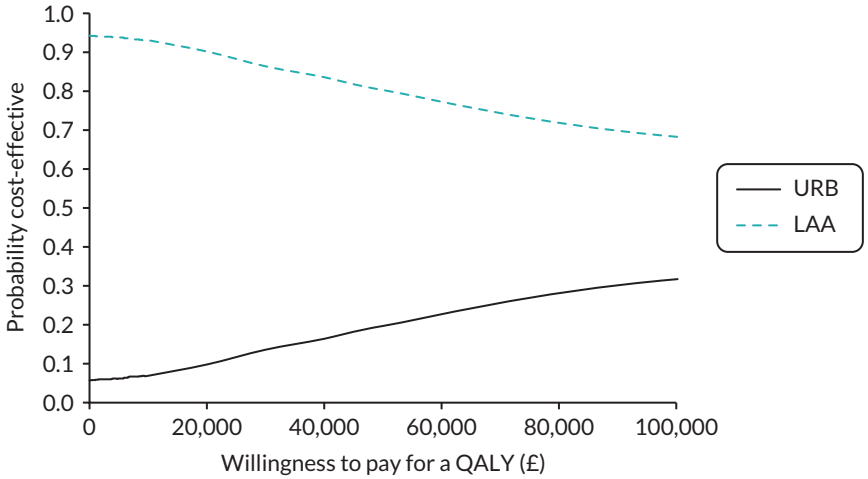

FIGURE 9 Cost-effectiveness acceptability curve for the complete case data for the CHU-9D.

Cost-consequence analysis

In addition to the CEA and CUA, a CCA comparing the costs to the secondary outcomes was carried out. The results can be seen in *Table 21*.

In addition to the CEA and CUA, a CCA comparing the costs to the secondary outcomes was carried out. The results can be seen in *Table 21*. The value representing the impact of each of the measures is derived from *Table 10* in the previous chapter. For the majority of outcomes there is no evidence of a difference, although for the majority of these the CI are wide enough to include clinically or economically important differences. The only measure where there was evidence of a difference was the RBQ Teacher Mean Total score, which favours the LAA intervention.

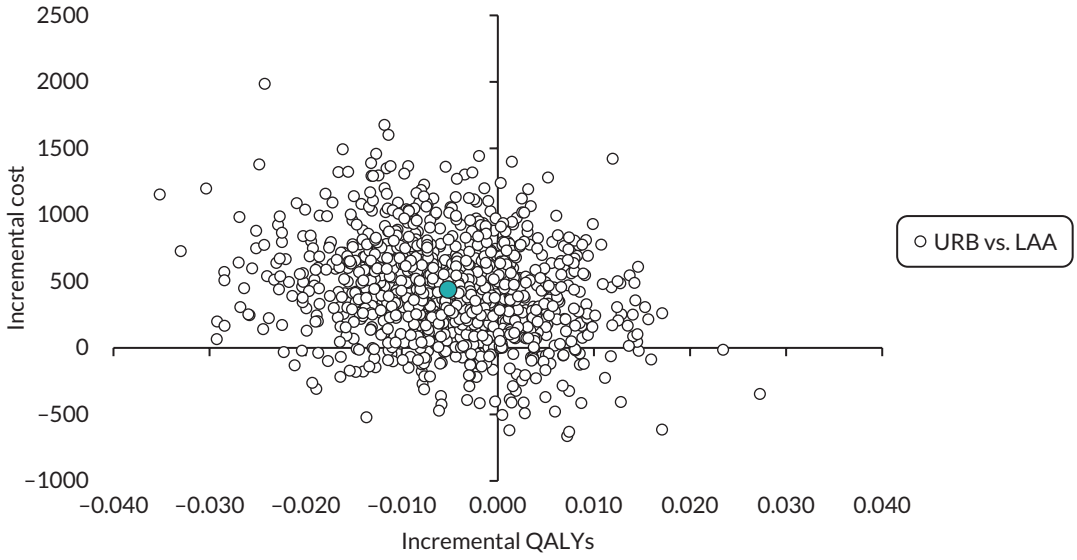

FIGURE 10 Cost-effectiveness plane for the imputed case data for the CHU-9D.

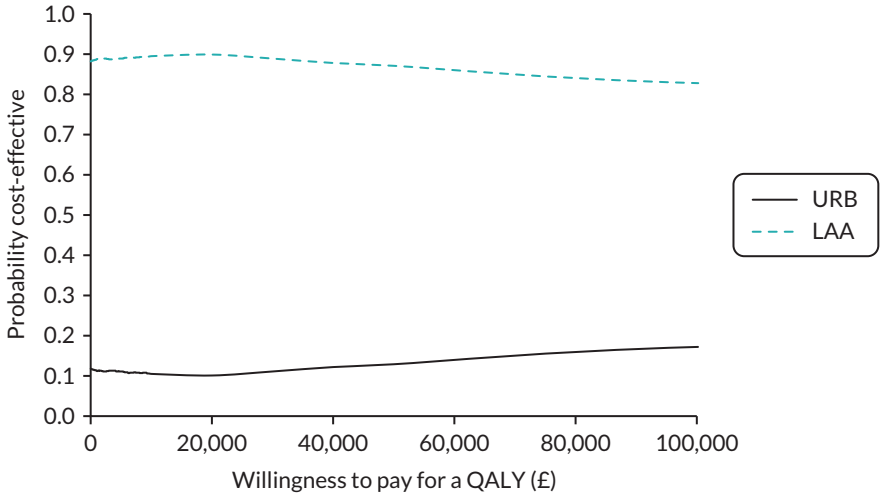

FIGURE 11 Cost-effectiveness acceptability curve for the imputed case data for the CHU-9D.

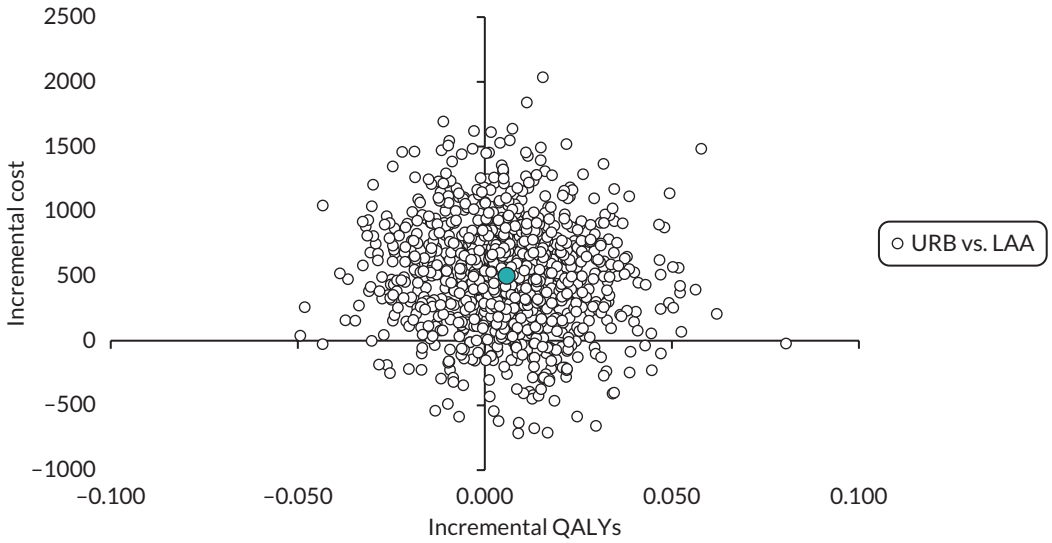

FIGURE 12 Costs-effectiveness plane for the imputed case data for the EQ-5D-5L including time, travel and private costs.

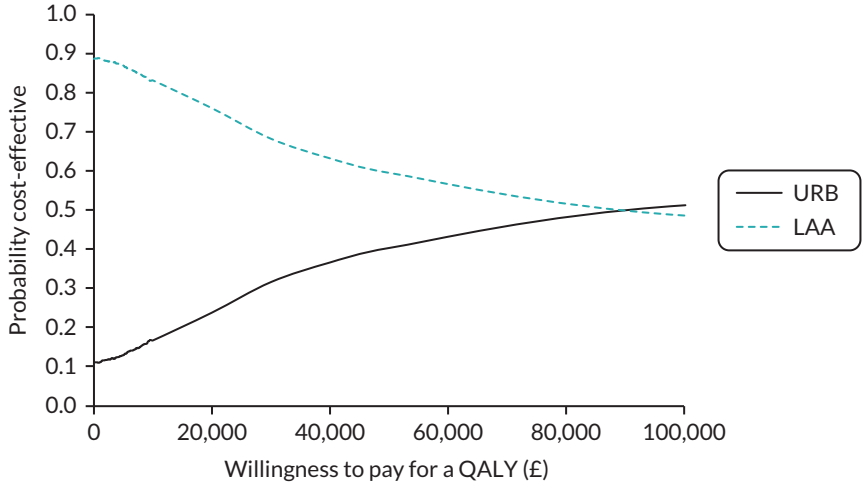

FIGURE 13 Cost-effectiveness acceptability curve for the imputed case data for the EQ-5D-5L including time, travel and private costs.

TABLE 21 Cost-consequence analysis of the LAA and URB intervention

Impacts that favour LAA		Impacts that favour URB	
Measure	**Value**	**Measure**	**Value**
RBQ Teacher Mean Total score. URB -LAA change from baseline at 52 weeks (95% CI)	0.18 (0.05 to 0.31)	–	–
No evidence of a difference			
Lower adjusted costs on average (95% CI)	£445 (−387 to 1278)		
RBQ-2 Sensory Motor Behaviour. URB-LAA change from baseline diff (95% CI)	−0.01 (−0.09 to 0.07)	VABS-3 Socialisation. URB-LAA change from baseline at 24 weeks (95% CI)	0.21 (−1.94 to 2.37)
RBQ-2 Insistence on Sameness. URB -LAA change from baseline at 52 weeks (95% CI)	0.02 (−0.08 to 0.12)	VABS-3 ABC. URB-LAA change from baseline at 24 weeks (95% CI)	0.2 (−1.28 to 1.68)
RBQ-2 Mean Total score. URB-LAA change from baseline at 52 weeks (95% CI)	0.01 (−0.06 to 0.09)	PSE. URB-LAA change from baseline at 52 weeks (95% CI)	0.19 (−0.07 to 0.44)
VABS-3 Communication. URB -LAA change from baseline at 24 weeks (95% CI)	−0.94 (−3.26 to 1.4)	APSI Total. URB-LAA change from baseline at 52 weeks (95% CI)	−0.81 (−3.2 to 1.59)
VABS-3 Daily Living Skills. URB -LAA change from baseline at 24 weeks (95% CI)	−0.32 (−2.32 to 1.65)	AFEQ Experience being parent. URB-LAA change from baseline at 52 weeks (95% CI)	0.17 (−1.5 to 1.85)
WEMWBS. URB-LAA change from baseline at 52 weeks (95% CI)	−1.3 (−3.45 to 0.86)	AFEQ Family life. URB -LAA change from baseline at 52 weeks (95% CI)	−0.04 (−1.39 to 1.32)
AFEQ Total. URB-LAA change from baseline at 52 weeks (95% CI)	0.34 (−3.45 to 4.12)		
AFEQ Child development understanding social relationships. URB-LAA change from baseline at 52 weeks (95% CI)	0.17 (−1.5 to 1.85)		
AFEQ Child symptoms. URB-LAA change from baseline at 52 weeks (95% CI)	0.74 (−0.39 to 1.86)		

Chapter 6 Discussion

The main aim of this multisite RCT was to assess the clinical and cost-effectiveness of the URB parent/carer group intervention versus a psychoeducation parent/carer group LAA for parents/carers of young autistic children aged 3 to 9 years 11 months, who present with functionally impactful RRB.

Families were recruited from clinical services across three research sites, two in the North of England and one in Scotland. Parents/carers were randomised to either URB or LAA and our analyses indicate that both interventions were run by trained facilitators with fidelity to the manuals. A small number of SAEs were noted for participants, none of which were deemed to be related to participation in the study, indicating that there were no identified serious risks associated with either intervention. Rates of and types of ESI were comparable across arms suggesting that any differences detected were not attributable to differences in families' circumstances or experiences during participation.

All children had previously received a clinical diagnosis of ASD. Autistic traits were assessed at baseline using a play-based observational assessment (the ADOS-2) and a parent/carer questionnaire (the SRS-2). Adaptive functioning was assessed using the VABS-3. The mean scores reported across all three ADOS-2 modules produced comparison scores of six, indicating 'moderate' levels of autism spectrum related symptoms which are representative of a clinical sample of autistic children. Given COVID-19 restrictions, only around two-thirds of the sample were able to complete the ADOS-2, which is an in-person assessment, so caution needs to be applied in using these data to describe the representativeness of the sample. SRS-2 scores indicated that the sample demonstrated characteristics that are strongly associated with a diagnosis of autism. The mean baseline ABC score (67.63), derived from the VABS-3, was within the 'low' range of adaptive functioning, indicating difficulties with adaptive behaviour and daily living skills that are consistent with a clinical sample of autistic children. For comparison to a wider sample, based on standardisation data, a mean score of 63.3 is reported for autistic children aged 3–8 with a concurrent intellectual disability and a mean score of 76.8 is reported for autistic children aged 3–8 without a concurrent intellectual disability. The range of scores reported for the SRS-2 and the VABS-3 ABC suggests a sample of autistic children with mixed abilities, including children with and without a concurrent intellectual disability.

Recruitment to and participation in the study was significantly impacted by the onset of the COVID-19 pandemic in March 2020. At this point, the study was still recruiting participants, running intervention groups in person, and undertaking all assessments directly with parents/carers and children. Following extensive discussion, a decision was made to continue with the trial, necessitating a number of significant procedural changes, with all consent and assessment visits moved to remote delivery (via telephone) and intervention groups delivered online using free-to-access platforms. The ADOS-2 assessment was no longer able to take place. The move to remote delivery of the study did not seem to have impacted significantly on total recruitment to the trial (though recruitment at the Lothian site was completely closed from March 2020 to the end of the recruitment window). It is apparent however that a number of families were lost to follow-up and the primary end point, with missing data for 72 families at this follow-up point. The primary clinical outcome for the study was the CGI-I scale at 24 weeks. The CGI-I comprised data from a range of sources, which captured the presence and impact of functionally impactful RRB (the vignettes), RRB more generally (the RBQ-2 and Teacher RBQ) as well as adaptive functioning (the VABS-3). An ITT analysis indicated that at the primary end point (24 weeks) there was no evidence of an intervention effect on CGI-I, blind rated by trained assessors. It is important to consider the findings in relation to statistical power. Despite good enrolment to the trial, at the primary end point, due to difficulties contacting families for follow-up, the primary analysis was underpowered with 31.72% missing data (power = 70–75%). CGI-I was also analysed on its original scale and the result was in agreement with the primary analysis (see *Appendix 3*, *Table 26*). Thus, there is inconclusive evidence that the URB intervention was more effective than the attentional control (LAA), when considering global improvement in child functioning.

The results of the economic evaluation demonstrate that the URB intervention is unlikely to be considered cost-effective when compared to an active comparator such as LAA. These findings align with a previous study, the original Paediatric Autism Communication Trial (PACT) which found that the PACT intervention (a parent-mediated communication-focused therapy) resulted in a small additional effect at a greater cost.[64] However, in keeping with the PACT, both studies demonstrated significant improvement in outcomes that are more proximal to the treatment

target of the intervention. Further analysis of the PACT data has highlighted both a significant difference between the intervention and treatment as usual (TAU) and also persistence of the benefit 6 years after the end of the study.[13] There are therefore a number of factors to consider around the interpretation of how best to evaluate both the clinical and cost-effectiveness of autism interventions which in turn can help inform future research in this area for autistic children and their families and the wider autism community.

We also considered the findings in relation to the secondary outcome measures. It is important to bear in mind two considerations when reflecting on the findings of the secondary outcomes. First, the study collected less than the expected data at the primary end point. Second, much of the study took place during a period of uncertainties, including for many the absence of their usual daily routines and support. Thus, taking part in the research study and having access to the support of a parent/carer group intervention may have provided participating families with a different experience from their peers.

The most proximal outcomes to the URB intervention are the TBVs, which capture a detailed description of a behaviour and its functional impact, from parent/carer interviews. Pairs of vignettes from different time points are then compared and expertly rated as indicating response/non-response. Our analysis demonstrated that children in the URB group were significantly more likely to be rated as responders at 10 and then at 24 weeks, with the odds of improvement in functionally impactful RRB on average 92% higher in the URB arm than the LAA arm at the primary end point (24 weeks). In addition, our analysis indicates that there was a statistically significant difference on impact on the family at 10 and 24 weeks, with those in the URB arm more likely to be rated as 'responders' than families in the LAA arm. These findings indicate that the URB intervention is more effective at supporting parents/carer to understand and reduce the impact of their child's functionally impactful RRB than the LAA intervention and the maintenance of that effect 6 months post intervention is also clinically meaningful.

Restricted and repetitive behaviour more generally were also captured using two questionnaire measures (RBQ-2 parent and RBQ-2 teacher). A significant difference in parent/carer-reported RRB between the arms was found at 10 weeks follow-up, with lower RRB scores reported for those in the URB arm compared to the LAA arm. However, closer inspection of the data suggests that the difference can be accounted for by an increase in reported sensory motor RRB by parents/carers in the LAA arm, rather than a decrease in scores in the URB arm, and this pattern is not apparent at subsequent time points. Our findings therefore indicate that when considering parent/carer report of RRB more generally, rather than one specific functionally impactful RRB, as captured in the vignettes described above, there is no advantage conferred by participation in the URB intervention. Similar conclusions must be drawn when considering general RRB rated by teachers (using the RBQ-2 Teacher total scores) where we find a significant difference in RRB between the two intervention arms at 52 weeks. Further inspection reveals that this can be accounted for by a significant decrease in scores in the LAA arm at 52 weeks compared to the baseline. There were no significant changes in teacher-rated RRB over time in the URB arm.

One possible interpretation of these self-report findings, in relation to the vignette-based results, is that the URB intervention was successful in having an impact on identifying and specifically moderating functionally impactful RRB. A more general reduction in RRB as a whole was not observed. It would be unwise to conjecture further without more knowledge of all the different RRBs exhibited by the autistic children in our sample, but certainly a general extinguishing of RRB should not be considered either the goal of this intervention, or a sign of success.

As can be seen from the results for the other clinical effectiveness secondary outcomes, there is a general trend towards improvement across a range of both child and parent/carer outcomes, within both intervention arms, but no significant differences between the arms, indicating that participation in either intervention (or professionally run parent groups in general) may be beneficial for parents/carers and families.

Child adaptive behaviour was captured using the VABS-3 at baseline and then again at 24 weeks. For the URB group, significant changes can be seen in the domains of daily living skills, socialisation and the composite score comparing the 24-week outcomes to the baseline. These improvements are also found for children whose parents/carers participated in the LAA group, with the addition of a significant improvement in the communications domain also. No significant differences were found between the arms, indicating that while gains in adaptive functioning over time are apparent,

these improvements are not specific to either intervention. It is also important to note that these changes, although statistically significant, are small and do not represent a clinically meaningful change in adaptive function.

Turning now to the parent/carer and family functioning measures, the story is similar. The PSE[37] was used to record the presence/absence of behaviours typically exhibited by autistic children and parents/carers' confidence in managing these behaviours. A significant difference between the arms was found on the PSE at 10 weeks follow-up, with the URB parents/carers reporting higher levels of self-efficacy compared to the baseline and to the LAA group, while the LAA group scores did not differ from the baseline. This difference between the arms is not maintained at 24 or 52 weeks follow-up; instead, within both arms we see significant increases in parent/carers self-efficacy compared to the baseline.

These findings are similar to those found with an APSI. Using the APSI, parenting stress can be seen to significantly reduce in the URB group at all follow-ups; for the LAA group no significant reduction was apparent at 10 weeks, but a significant reduction was apparent by 24 weeks and maintained at 52 weeks. There are no detected differences between the arms at any time point. Across these two measures then, we see more immediate positive impacts on the PSE and stress in the URB group, but over a longer time period both parent/carer groups yield benefits in this domain.

Parental well-being was further assessed using the WEMWBS at 24 and 52 weeks. No significant differences were found comparing the URB and LAA arms at either time point. Within the arms, a significant favourable change in scores was found for both arms at 52 weeks, but not at 24 weeks.

The AFEQ provides an overview of the family experiences of families including an autistic child. It provides scores within four domains [experience of being a parent/carer; family life; child development, understanding and social relationships; child symptoms (feelings and behaviour)] as well as a total score. For the family life and child development domains, significant changes are present at 24 weeks and 52 weeks for the URB arm, whereas a significant change only becomes apparent at 52 weeks for the LAA arm. For child symptoms there are no significant findings within or between arms at any time point.

Taken together, the findings from the secondary measures relating to parental functioning (self-efficacy, stress and well-being) and family functioning suggest that for the families that participated in the study both intervention programmes yielded positive outcomes, with no statistically significant differences between the two approaches. The results highlight that both the URB and the LAA interventions (or professionally delivered parent/carer groups) have the potential to be generally beneficial to families of young autistic children experiencing functionally impactful RRB. Of course, these were the families who had agreed to take part in the research. The continuity of being part of the trial especially during a time of great uncertainty for families and the wider community may have also been relevant.

It is important to reflect on potential explanations for the lack of positive effect of the URB intervention on the primary outcome (CGI-I) at the primary end point. A number of, potentially interrelated, explanations are worthy of consideration, including the suitability of the primary outcome to detect a difference, the suitability of the primary end point (24 weeks), the lack of statistical power to detect an effect (due to missing data) and of course the possibility that our hypothesis that URB would be superior to LAA is incorrect.

Regarding the suitability of the primary outcome and end point, the CGI-I measure was selected as it was in keeping with the priorities of the autism community in that it is a measure that captures global functioning that is relevant to everyday life experiences. In addition, this outcome was used during the pilot study and has been widely used in other clinical trials with autistic children and their families. However, the aim of both interventions was not to reduce the symptoms of autism, and also our understanding on whether and how changes in overall RRBs (including those considered to have a functional impact) might have affected global functioning is a complex judgement especially when the context for many families changed dramatically during the COVID-19 pandemic. Further, published early social communication intervention studies with autistic children often target proximal behaviours such as joint attention or parental synchrony. In such studies, a theoretical developmental framework supposes that gain of required proximal skills would lead to downstream impacts on wider abilities. This theoretical positioning reduces the burden on such trials to demonstrate either longer-term impact or change in measures of broader skills and everyday functioning. In contrast, the study's primary outcome relied on evidence of change not only in the proximal outcome (target vignette)

but across a range of domains (SCQ, VABS and parent/carer and teacher-reported RBQ). At the primary end point we do find a significant difference between the two arms in relation to the TBVs, the most proximal measure to the intervention, in favour of the URB arm. This short-term change in proximal skills corresponds with primary end points in other early autism intervention trials and suggests that 24 weeks may have been too early to detect evidence of broadening real-life impact.

With respect to the measures of health status used within the economic evaluation, the EQ-5D-5L is the recommended instrument by regulatory bodies such as NICE in their guidelines for health technology appraisals to express outcomes in terms of QALYs[50] is not appropriate to measure health-related quality-of-life impacts of children aged under 12 years. It was utilised here to measure quality of life for the caregiver of the autistic child. There is an alternative version of the EQ-5D, the EQ-5D-Y that can be used to elicit health-related quality of life of younger children. However, it currently does not have a validated scoring system. Therefore, we used another tool, the CHU-9D, to estimate the impacts on health-related quality of life of younger children. Both the responses to the EQ-5D-5L and CHU-9D were used to estimate QALYs for parents/carers and children, respectively. The utility valuations that underpin the estimation of QALYs for both the EQ-5D and the CHU-9D only reflect health on the day that the measurements were completed. Brazier *et al.* noted that there are important elements of health that are not fully encompassed within the EQ-5D-5L (or CHU-9D) including well-being and capabilities.[65] Some of these impacts of interventions to help understand and respond to RRB may fall within this purview. These include such things as parental reassurance and changes in the ability to plan for the future. Future research could potentially utilise tools such the ICECAP-A approach[66] to measure parental QALYs from a capability and well-being approach. The view is supported by a recent review of economic evaluation approaches for children with neurodevelopmental disorders which advocates for greater use in approaches such as the capability approach.[67]

In addition to utilising well-being and capability approaches, there are also future opportunities to assess benefits from such interventions within the context of a cost–benefit approach. Potential options include the use of contingent valuation methods, which allow participants to value the intervention in monetary terms. The advantage of this approach is it allows respondents to consider all the facets of the intervention as they value it. While there are challenges in using this approach to value health care, a similar approach has been used to value early intervention for those with dementia.[68] Exploring differing approaches to valuing interventions for the parents/carer of autistic children could form the basis of future research.

Another consideration regarding the results of the economic evaluation is the time horizon for the study, which in this case was 52 weeks. As this was a parenting intervention it is possible that the timescale of benefits (and cost) could extend into the future as the child grows into an adolescent and an adult. As such, a longer period of follow-up would be welcomed. This would provide an opportunity to consider the perspective of the autistic adult which is an understandable high priority of the autism community.[69,70] Further, this would also provide a mechanism to examine any long-term harms of the intervention, something that is rarely done.[69] It can be difficult to measure longer-term outcomes within the context of a trial. However, using other study designs such as observational approaches could provide valuable information to inform a cost-effectiveness modelling approach. The modelling approach could adopt a much longer time horizon, such as 20 years, or a lifetime time horizon to truly understand the long-term impacts of such early years' interventions.

While our fidelity assessment indicated that both interventions were successfully delivered with fidelity to their respective manuals, with different therapists involved in each arm of the trial, there is the possibility of inadvertent personalisation and informal discussion of RRB by therapists in the LAA arm. Some personalisation was noted within the LAA arm during fidelity checks, possibly due to small group numbers (i.e. one or two parents/carers in attendance) and therapists' desire to support families during the COVID-19 pandemic. This would, of course, reduce the potential difference between the content of the two interventions and increase the sample required to detect any effect, in what is already an underpowered trial.

This study has a number of strengths. The URB intervention was developed in partnership with parents/carers in response to an identified underserved clinical need and contributes significantly to the range of interventions available to parents/carers of autistic children by providing the first manualised parent/carers mediated intervention that focuses

on functionally impactful RRB. Despite the challenges and restrictions of COVID-19, the clinical and research teams responded rapidly to the unfolding situation and adapted research methods and clinical delivery to enable the trial to continue to deliver the study objectives, with recruitment closing permanently in only one research site (Lothian). One unanticipated benefit of these challenging circumstances was the opportunity to deliver the assessments and interventions via remote means. Our fidelity analysis, which included ratings of sessions delivered in the original face-to-face and remote formats, indicates that both methods of delivery are feasible, can be done with fidelity to the manual and are acceptable to parents/carer. Indeed, informal feedback from parents/carers during COVID-19 suggests that they were appreciative of the efforts of the research and clinical teams to continue with the study during a time when many clinical, educational and support services were closed.

On the other hand, only a minority of families (n = 47) completed their participation in the trial up to the 24-week follow-up assessment entirely prior to the onset of COVID-19 restrictions and therefore less than 25% of those families recruited to the study experienced the trial in its original format. For all other families, a combination of arrangements was in place. Some families had baseline assessment pre COVID-19 and all other procedures (intervention and follow-up assessments) during COVID-19 restrictions, while others had baseline assessment and participated in their intervention pre COVID-19 and then completed the primary end-point follow-ups during COVID-19 restrictions and some had all study procedures during COVID-19 restrictions. It is impossible to determine the precise impact of these unanticipated and fluctuating circumstances on the families who were part of the study, or indeed on the research and clinical team charged with delivering the trial in such uncertain times. Although the study recruited and randomised 227 families, a significant number were lost to follow-up at the 24-week primary end point and it is plausible that COVID-19 contributed substantially to this attrition rate.

Coronavirus-19 may also have impacted in other ways on the outcomes of the study. Many parents/carers reported changes in their child's well-being as a consequence of the pandemic. For some, these changes may have been difficult, with an increase in worry and anxiety related to the uncertainty about how the pandemic would unfold and disruptions to routine. For others, the changes may have been more positive with the child benefiting from a less demanding lifestyle with the focus on staying at home with family. For many families it may have been a combination of the two at different times.[71,72] For all parents/carers the closure of schools and other services meant that they lost their expected everyday support networks and often became sole full-time caregivers of their autistic child. In the context of these difficult uncertain and changing circumstances, the significant and positive changes detected in parental self-efficacy, well-being and stress and the improvements in family functioning in both arms are not to be underestimated.

Statistical considerations

Please see *Chapter 2*, *Statistical Methodology* where the COVID-19 implications on statistical analyses are discussed.

Equality, diversity and inclusion and patient and public involvement

Recruitment via clinical teams and data from available baseline characterisation measures indicates that the sample was comprised of autistic children with mixed abilities, including children with and without a concurrent intellectual disability. This is consistent with our inclusion criteria (no restrictions based on ability). The age range for children eligible for the study was widened in response to feedback from clinical teams that the intervention was needed for older children too. In collaboration with PPI advisers, we ensured that participant-facing documents were inclusive and accessible. Parent/carer group sessions were purposefully offered in areas of economic deprivation to support participation of families from these areas. Despite recruiting from a relatively large geographical area, the sample was not representative of the ethnic diversity across the UK. Indeed, one reason given for declining to take part in the study was the lack of availability of translators. The majority of children were from white ethnic backgrounds (85.9%). This is consistent with research indicating that there is a need for more culturally responsive practices for autistic people. Future research should aim to actively explore any potential reasons why families from non-white backgrounds are under-represented and promote recruitment polices that aim to rectify this imbalance and incorporate issues relating to diversity into research questions.[73]

Our research team comprised of individuals from a range of cultural and ethnic backgrounds, as well as those with lived experience. The research staff involved in the study benefited from training on a range of clinical measures and research and statistical techniques and some have now progressed to clinical training and others to research posts. Opportunities were provided for undergraduate students and trainees to work as interns during the study, gaining valuable skills and knowledge to further their career prospects.

Patient and public involvement

Parent/carer representatives were involved in the initial development of the URB programme (see *Introduction*), as well as acting as full and active members of the TSC. PPI considerations are also embedded within our dissemination strategy. We have established a working group and are in the process of developing guidelines for how to proactively engage with the autism community in relation to the interpretation and dissemination of the findings of the study. Outputs will be guided by close liaison with PPI advisers to ensure that the materials are accessible and inclusive, and that the language is appropriate. For example, outputs will be sensitivity-read by paid, autistic sensitivity readers. Conference presentations will include contributions from PPI representatives. Working closely with our PPI parent advisers and representatives from the autism community, we are planning a series of dissemination events and publications for the wider autism and more general community, in addition to academic and clinical outputs. For example, a URB newsletter for parents/carers, clinicians and local stakeholders who helped with recruitment will be produced and distributed at all sites. PPI representatives, with support from the research team, will submit an article to the INVOLVE newsletter and we hope to be able to present the study findings at appropriate parent/carer/third sector/professional local, national and international conferences including NAS Annual Conference, Autism Europe, and the International Society for Autism Research (INSAR). We will publish a FAQ on the URB website that addresses questions from the autistic community. We will also host a free, online 'town hall' event after publishing results where autistic people, and anyone from the broader autism community, can come and ask questions from a panel of the research team. Reports will be submitted in accessible newsletters such as Your Autism and Your Impact (NAS) and Asperger United. A feedback event will be held which will be available across all sites.

The novel URB intervention evaluated in this trial was developed over 12 years ago and piloted almost 10 years before the publication of this report. In that time there has been an explosion in recognition of the imperative, and understanding of how, to work with autistic people as partners in research (Fletcher-Watson *et al.* 2019, 2021). Reporting the results of this trial provides an important point at which to engage with the autism community – not only parents/carers and practitioners, who already have played key roles in the creation of URB and its evaluation, but also autistic people. While many decisions are in the past, there is room for autistic influence in interpreting and sharing these findings and determining the appropriate next steps for research and practice. We will be convening a consultant group to partner with us in this work. It is already clear that future research should work with autistic people to examine how we distinguish between RRB that are/are not reasonable targets for intervention, and what alternate strategies for managing anxiety and distress might be most useful for autistic children to adopt.[74,75]

Limitations

- The study did not recruit to target, and experienced high attrition at follow-up. The study was therefore underpowered at the primary end point to detect a difference between the two arms.
- The study employed a number of retention strategies that were unfortunately not successful. The retention strategies employed included consideration of parent burden in selection of outcome measures, frequent family newsletters reporting on study progress, follow-up assessments where possible being completed by the same RA so a rapport could be built up, flexibility in timings and location of follow-up assessments, reminder texts, e-mails, letters and phone calls.
- Delivery of the trial was significantly impacted by the onset of COVID-19. It is not possible to determine whether the change of delivery methods impacted on the findings reported.
- There is a lack of ethnic diversity amongst the families who participated in the study.

- Although no measure of co-occurring problems was included in the study protocol, the range of scores reported for the SRS-2 and VABS-3 ABC subscale provided indirect markers of the range of difficulties commonly experienced by young autistic children.
- Direct observational assessment of the children was not possible following onset of the COVID-19 pandemic.
- The follow-up of the study may have been too short to detect differences in effectiveness and cost-effectiveness of the interventions.
- An ongoing methodological challenge is that there is no single measure or methods to aggregate health status and QALYs across carers and child.

Measures of health status themselves may not reflect the broader impacts of the interventions. Other outcomes such as those relating to the ICECAP may be worth exploring in future studies.

There is a lack of any qualitative work such as a process evaluation to help explore potential explanations for the limited effectiveness of the URB parent group. Qualitative semistructured interviews may have provided insights into low attendance rates and factors that impacted on recruitment and retention rates.

Strengths

- Families were successfully recruited from a range of clinical services across three research sites.
- Adaptations to delivery of both research assessments and the two parent group-based interventions were possible to enable the study to continue despite restrictions related to the pandemic. However, a great deal of additional work was required by the research team and the therapists as each NHS trust adopted different virtual packages based on local policies/guidance.
- Trained facilitators were able to deliver the programmes with fidelity to the manuals in both in-person and remote formats. A very small number of unrelated SAEs were noted indicating that there were no identified risks associated with either intervention.
- The economic evaluation used rigorous, widely accepted and explicit methods to estimate relative efficiency. This was done in three complementary ways, accompanied by extensive stochastic and deterministic sensitivity analysis which gave rise to broadly consistent conclusions.

Implications for practitioners

- Our data suggest that those parents/carers who took part in the research found both interventions to be helpful, feasible and acceptable, and we demonstrated that both can be delivered with fidelity to the manual in in-person and remote formats.
- Many parents/carers did not take part in the research citing a range of reasons including time commitments, child care, finances, and travel arrangements. Those who did take part during the COVID-19 pandemic found face-to-face and online delivery of the parent group intervention, and telephone assessment appointments acceptable. Providing carefully tailored and flexible opportunities for families to attend appointments for assessments and/or access to interventions may improve efficient use of limited clinical resources without necessarily impacting of quality-of-service delivery.
- The use of online delivery for both parent groups was found to be acceptable and feasible. Online delivery can increase efficiency in a variety of ways for both parents and healthcare professionals.
- Some families who declined to take part indicated that they could not identify any functionally impactful RRBs. The discussion about RRBs and social communication needs are important as part of the diagnostic assessment process and when planning appropriate interventions to meet the needs of young autistic children and their families.

Implications for parents/carers and autistic children

- Participation in the URB programme resulted in a greater likelihood of reduction in engagement in functionally impactful RRB by the child and an improvement in the impact of those functionally impactful RRB on the family.

- Parents/carers who attended URB and LAA reported an increase in self-efficacy, a reduction in parenting stress and improvement in well-being over time indicating that both programmes are helpful to parents/carers of young autistic children.
- Participation in either the URB or LAA parent groups can be mutually beneficial and supportive for parents of autistic children.
- A flexible approach to the timely delivery of both assessments and interventions with opportunities for face-to-face and/or virtual delivery of services was acceptable to parents/carers who took part in this research.

Implications for research

In future research it will be important to determine:

- How can participation in autism research of autistic people from non-white backgrounds be improved? Issues relating to diversity should be built into research questions.
- What are the mechanisms of change in functionally impactful RRB?
- What should be included in a standardised set of outcome measures for autism intervention studies and what should be the optimal primary end point to detect meaningful change?
- How can recruitment and retention of families be improved?
- How can attendance rates at parent group sessions be improved?
- Whether longer longitudinal follow-up, which could be utilised in economic modelling studies over a longer time horizon, could change conclusions on effectiveness and cost-effectiveness.
- What other measures could be used to quantify benefit for economic evaluations in autism intervention studies?

Chapter 7 Conclusion

The study unfortunately collected fewer than expected data at follow-up assessment time points and therefore findings related to the potential clinical effectiveness of URB remain inconclusive. From a cost-effectiveness perspective, although the evidence in this study demonstrated that URB was unlikely to be considered cost-effective at 12 months, future research in this area could potentially focus on a longer longitudinal follow-up, which could be utilised in economic modelling studies over a longer time horizon. In addition, different approaches to measuring benefit for parent/carer interventions for autistic children could be utilised to capture both potential positive change and adverse outcomes that are relevant to both autistic children and to the families of autistic children and meet the priorities of the autism community. These should include relevant non-health effects.

Additional information

Contributions of authors

Victoria Grahame (https://orcid.org/0000-0003-4541-7574) (Chief Investigator) designed the study, was principal applicant for funding, wrote the study protocol, supervised the overall conduct of the study, interpreted study data and co-wrote the final report.

Ashleigh Kernohan (https://orcid.org/0000-0002-5514-3186) (Health Economist) aided with the design of the study, analysed and interpreted the data and co-wrote the final report.

Ehsan Kharati (https://orcid.org/0000-0002-4439-6751) (Statistician) designed the statistical analysis plan, co-wrote the statistical methodology in the study protocol, conducted the main study analysis, interpreted the study results and co-wrote the final report.

Ayesha Mathias (https://orcid.org/0000-0001-7852-6342) (Trial Manager) provided day-to-day management of trial conduct, contributed to the study protocol, performed monitoring to ensure the trial was conducted to Good Clinical Practice requirements, edited and co-wrote the final report.

Chrissie Butcher (https://orcid.org/0000-0002-1696-1506) (Senior Trial Manager) supervised day-to-day management of trial conduct and co-wrote the report.

Linda Dixon (https://orcid.org/0000-0001-9376-8331) (Co-applicant) contributed to design intervention, provided clinical supervision and delivered training to all therapists.

Sue Fletcher-Watson (https://orcid.org/0000-0003-2688-1734) (Co-applicant and research lead) contributed to design, supervised RAs, helped interpret results and co-wrote the final report.

Deborah Garland (https://orcid.org/0000-0002-3708-4186) (Co-applicant) parent representative, led training and delivery of the LAA comparative arm of study.

Magdalena Glod (https://orcid.org/0000-0001-5798-0044) (RA at Newcastle University) contributed to day-to-day running of the trial at Newcastle and reviewed the final report.

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Emma Honey (https://orcid.org/0000-0001-7016-9096) (Previous PI and Co-applicant at CNTW) contributed to day-to-day running of the trial at Newcastle and reviewed the final report.

Ann Le Couteur (https://orcid.org/0000-0001-9991-3608) (Co-applicant at Newcastle University) contributed to the design, contributed to the study protocol, interpreted the results and co-wrote the final report.

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Emmanuel Ogundimu (https://orcid.org/0000-0001-9252-9275) (Senior Statistician) co-designed the main study analysis, co-wrote the statistical methodology in the final report, interpreted the results and co-wrote the final report.

Helen Probert (https://orcid.org/0009-0001-7364-024X) (RA at Durham University) contributed to day-to-day running of the trial at Durham and reviewed the final report.

Deborah Riby (https://orcid.org/0000-0001-5747-8441) (Research Lead and Co-applicant at Durham University) contributed to the design, supervised RAs and co-wrote the final report.

Priyanka Rob (https://orcid.org/0000-0001-9039-8099) (RA at CNTW and TEWV) contributed to day-to-day running of the trial at Newcastle and Durham and reviewed the final report.

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Christopher Weetman (https://orcid.org/0000-0002-6372-0393) (Database Manager) managed the data entered by centres as well as central data processes, enabled data cleaning and edited the final report.

Jacqui Rodgers (https://orcid.org/0000-0002-1759-316X) (Co-applicant, Research Lead and interim CI at Newcastle University) contributed to the design of the study, contributed to the study protocol, supervised the overall conduct of the study, interpreted study data and co-wrote the final report.

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Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure to protect everyone's privacy and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data may be granted following review.

Ethics statement

This trial received ethical approval on 20 August 2018 from the South West – Plymouth and Cornwall Ethics Committee: 18/SW/0173.

Information governance statement

Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, CNTW is the data controller, and you can find out more about how we handle personal data, including how to exercise your individual rights, and the contact details for our Data Protection Officer are here: www.cntw.nhs.uk/foi/data-protection/.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/WHTU0367.

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Publications

Grahame V, Dixon L, Fletcher-Watson S, Garland D, Glod M, Goodwin J, *et al*. A clinical and cost-effectiveness trial of a parent group intervention to manage challenging restricted and repetitive behaviours in young children with autism spectrum disorder: study protocol for a randomised controlled trial. *Trials* 2021;**22**(1):240.

Grahame V, Kernohan A, Kharati E, Mathias A, Butcher C, Dixon L, *et al*. Understanding Repetitive Behaviours: A clinical and cost-effectiveness, multi-site randomised controlled trial of a group for parents and carers of young autistic children. *Autism* 2025;**29**(8):1998–2015. https://doi.org/10.1177/13623613251333175

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Appendix 1 Summary of second parent demographics and child baseline ADOS 2 scores

TABLE 22 Summary of parent 2 demographics

Variable	LAA *n/N* (%)	URB *n/N* (%)	Total *n/N* (%)
Parent 2 ethnicity			
Any white background	84/97 (86.6%)	87/98 (88.78%)	171/195 (87.69%)
White and Black Caribbean	0/97 (0%)	0/98 (0%)	0/195 (0%)
White and Black African	1/97 (1.03%)	0/98 (0%)	1/195 (0.51%)
White and Asian	1/97 (1.03%)	0/98 (0%)	1/195 (0.51%)
Any other mixed background	1/97 (1.03%)	0/98 (0%)	1/195 (0.51%)
Indian	0/97 (0%)	1/98 (1.02%)	1/195 (0.51%)
Pakistani	2/97 (2.06%)	2/98 (2.04%)	4/195 (2.05%)
Bangladeshi	1/97 (1.03%)	2/98 (2.04%)	3/195 (1.54%)
Any other Asian background	1/97 (1.03%)	0/98 (0%)	1/195 (0.51%)
Caribbean	0/97 (0%)	0/98 (0%)	0/195 (0%)
African	6/97 (6.19%)	4/98 (4.08%)	10/195 (5.13%)
Any other African background	0/97 (0%)	0/98 (0%)	0/195 (0%)
Chinese	0/97 (0%)	1/98 (1.02%)	1/195 (0.51%)
Any other ethnic group	0/97 (0%)	1/98 (1.02%)	1/195 (0.51%)
Missing	16/113 (14.16%)	16/114 (14.04%)	32/227 (14.1%)
Parent 2 marital status			
Single	8/95 (8.42%)	19/98 (19.39%)	27/193 (13.99%)
Married	66/95 (69.47%)	57/98 (58.16%)	123/193 (63.73%)
Civil partnered	1/95 (1.05%)	5/98 (5.1%)	6/193 (3.11%)
Separated (marriage or CP)	3/95 (3.16%)	2/98 (2.04%)	5/193 (2.59%)
Divorced/dissolved civil partnership	1/95 (1.05%)	1/98 (1.02%)	2/193 (1.04%)
Widowed/surviving civil partner	0/95 (0%)	0/98 (0%)	0/193 (0%)
Other	16/95 (16.84%)	14/98 (14.29%)	30/193 (15.54%)
Missing	18/113 (15.93%)	16/114 (14.04%)	34/227 (14.98%)
Parent 2 job			
Managers and senior officials	11/96 (11.46%)	7/98 (7.14%)	18/194 (9.28%)
Professional occupations	19/96 (19.79%)	20/98 (20.41%)	39/194 (20.1%)
Associate professional and technical occupations	12/96 (12.5%)	13/98 (13.27%)	25/194 (12.89%)
Administrative and secretarial occupations	2/96 (2.08%)	2/98 (2.04%)	4/194 (2.06%)

TABLE 22 Summary of parent 2 demographics (*continued*)

Variable	LAA *n/N* (%)	URB *n/N* (%)	Total *n/N* (%)
Skilled trades occupations	8/96 (8.33%)	16/98 (16.33%)	24/194 (12.37%)
Personal service occupations	8/96 (8.33%)	4/98 (4.08%)	12/194 (6.19%)
Sales and customer service occupations	2/96 (2.08%)	7/98 (7.14%)	9/194 (4.64%)
Process, plant and machine operatives	6/96 (6.25%)	6/98 (6.12%)	12/194 (6.19%)
Elementary occupations	7/96 (7.29%)	6/98 (6.12%)	13/194 (6.7%)
Full-time parent (never worked)	2/96 (2.08%)	4/98 (4.08%)	6/194 (3.09%)
Full-time student	0/96 (0%)	0/98 (0%)	0/194 (0%)
Unemployed	4/96 (4.17%)	7/98 (7.14%)	11/194 (5.67%)
Retired	2/96 (2.08%)	0/98 (0%)	2/194 (1.03%)
Not known	5/96 (5.21%)	1/98 (1.02%)	6/194 (3.09%)
Other	8/96 (8.33%)	5/98 (5.1%)	13/194 (6.7%)
Missing	17/113 (15.04%)	16/114 (14.04%)	33/227 (14.54%)
Parent 2 educational qualification			
None	6/101 (5.94%)	1/101 (0.99%)	7/202 (3.47%)
1–4 passes at CSE, GCSE, O-level	7/101 (6.93%)	12/101 (11.88%)	19/202 (9.41%)
5 or more passes at CSE, GCSE, O-level	17/101 (16.83%)	23/101 (22.77%)	40/202 (19.8%)
A levels or equivalent	25/101 (24.75%)	31/101 (30.69%)	56/202 (27.72%)
University	24/101 (23.76%)	23/101 (22.77%)	47/202 (23.27%)
Postgraduate degree	11/101 (10.89%)	8/101 (7.92%)	19/202 (9.41%)
Not applicable	1/101 (0.99%)	0/101 (0%)	1/202 (0.5%)
Don't know	10/101 (9.9%)	3/101 (2.97%)	13/202 (6.44%)
Missing	12/113 (10.62%)	13/114 (11.4%)	25/227 (11.01%)

TABLE 23 Summary of ADOS-2 baseline scores

Variable	*N* (missing)	Mean (SD)	Range	*N* (missing)	Mean (SD)	Range	*N* (missing)	Mean (SD)	Range
Module 1	37 (0)	16.73 (5.36)	7–27	26 (0)	16.92 (5.66)	5–26	63 (0)	16.81 (5.44)	5–27
Module 2	20 (1)	11.9 (3.78)	3–20	27 (1)	10.3 (4.32)	1–17	47 (2)	10.98 (4.14)	1–20
Module 3	24 (1)	9.83 (4.98)	2–18	21 (0)	11.43 (3.85)	4–19	45 (1)	10.58 (4.52)	2–19

The values of ADOS-2 scores across all three modules, and both trial arms, produce comparison severity scores of 6, indicating moderate levels of autism spectrum related symptoms which is consistent with a clinical sample of children with ASD (comparison scores are calculated ranging from 1 to 10, with scores of 1–2 indicating minimal to no evidence, 3–4 low, 5–7 moderate and 8–10 high levels of autism spectrum-related symptoms).

Appendix 2 Reasons for missing primary end-point at 24 weeks, summary of SAES

TABLE 24 Reasons for missing primary end point at 24 weeks

Reasons	Numbers
Did not attend any parent group session	11
Withdrawal or lost to follow-up	46
Week 24 visit not done	14
CGI-I rate not obtained	1

TABLE 25 Serious adverse event summary

	LAA	URB	Total
Variable	***n/N* (%)**	***n/N* (%)**	***n/N* (%)**
Who for			
Parent/carer	0/2 (0%)	2/3 (66.67%)	2/5 (40%)
Child	2/2 (100%)	1/3 (33.33%)	3/5 (60%)
Missing	0/2 (0%)	0/3 (0%)	0/5 (0%)
Severity			
Mild	2/2 (100%)	0/3 (0%)	2/5 (40%)
Moderate	0/2 (0%)	2/3 (66.67%)	2/5 (40%)
Severe	0/2 (0%)	1/3 (33.33%)	1/5 (20%)
Death	0/2 (0%)	0/3 (0%)	0/5 (0%)
Missing	0/2 (0%)	0/3 (0%)	0/5 (0%)
Causality			
Yes	0/2 (0%)	0/3 (0%)	0/5 (0%)
No	2/2 (100%)	3/3 (100%)	5/5 (100%)
Missing	0/2 (0%)	0/3 (0%)	0/5 (0%)
Hospitalisation			
Yes	2/2 (100%)	3/3 (100%)	5/5 (100%)
No	0/2 (0%)	0/3 (0%)	0/5 (0%)
Missing	0/2 (0%)	0/3 (0%)	0/5 (0%)
Outcome			
Recovered	2/2 (100%)	1/2 (50%)	3/4 (75%)
Condition improved	0/2 (0%)	1/2 (50%)	1/4 (25%)
Missing	0/2 (0%)	1/3 (33.33%)	1/5 (20%)

Plots for Clinical Global Impression improvement

It can be seen from the figures that there were a very small number of observations in subgroups, hence we have not performed the age subgroup analysis.

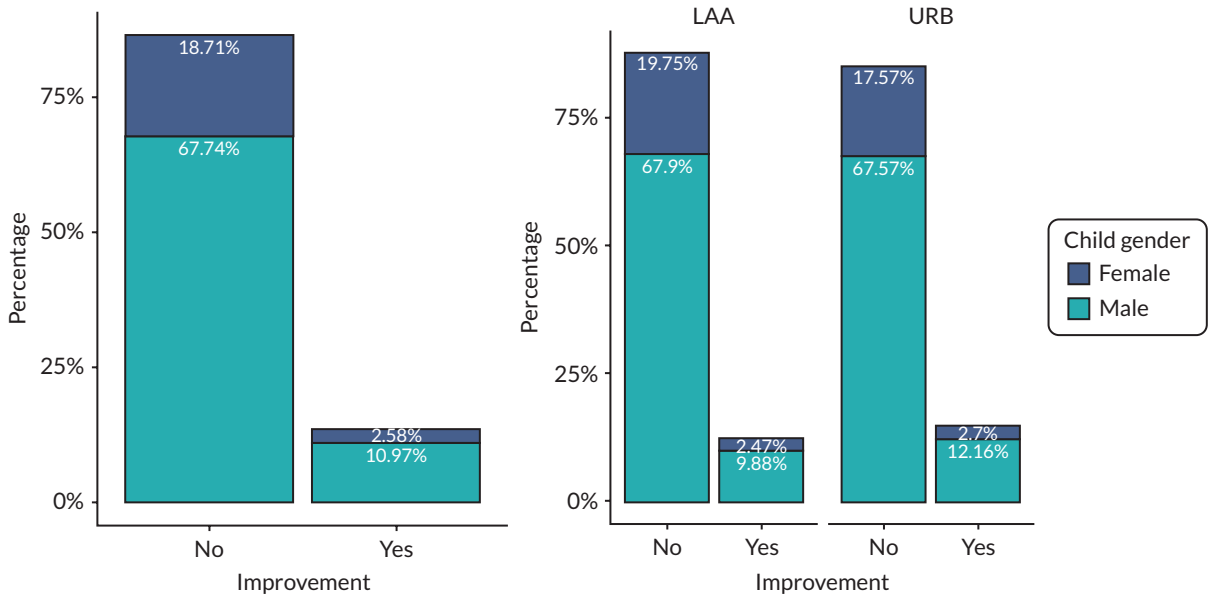

FIGURE 14 The percentage of improvement according to CGI-I within gender.

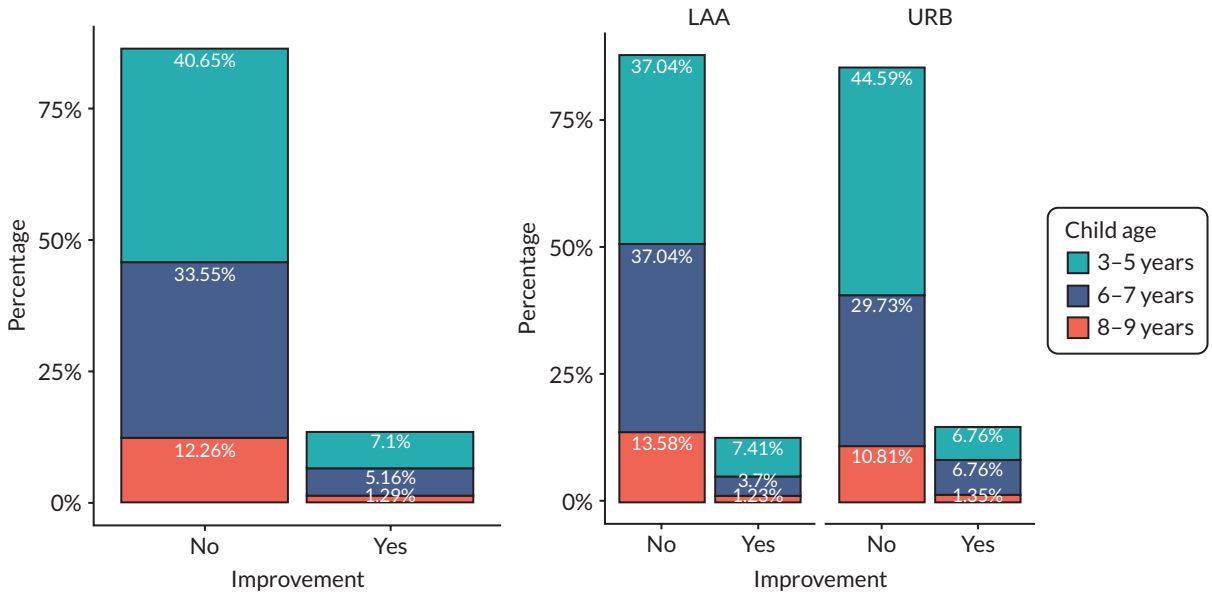

FIGURE 15 The percentage of improvement according to CGI-I within age.

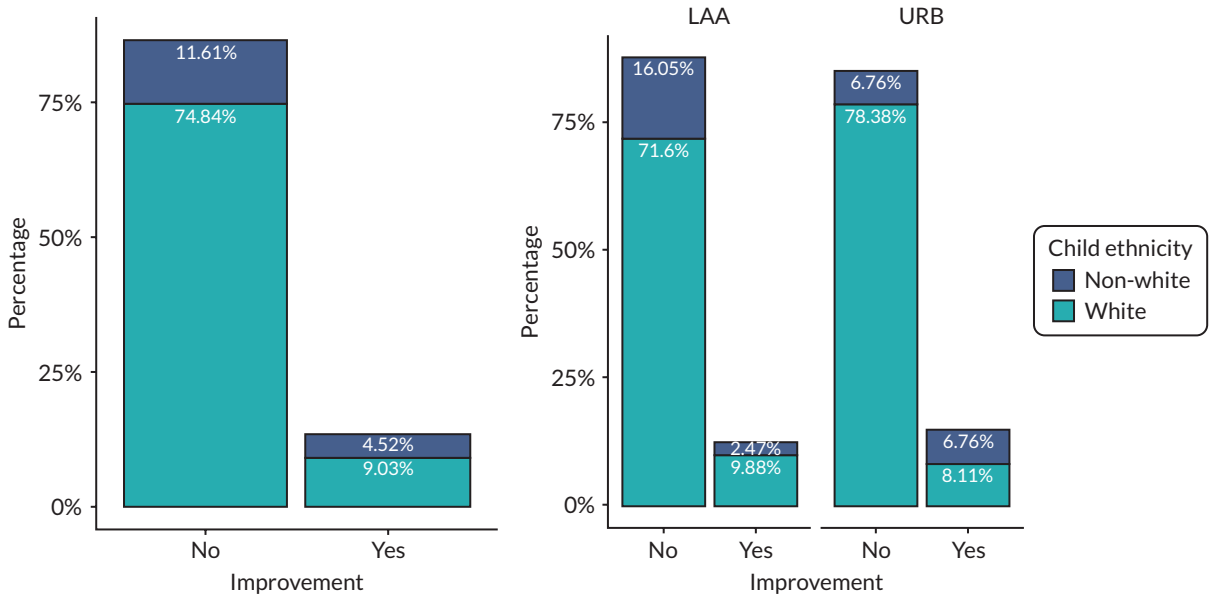

FIGURE 16 The percentage of improvement according to CGI-I within ethnicity.

Appendix 3 Plots for CGI-I improvement

We explored the percentage of improvement according to CGI-I for gender, age categories and ethnicity of the children in *Figures 14–16*. All comparisons here are exploratory with no formal statistical test. The rate of improvement in male is 11.0 while that of female is 2.6%. Of note is the fact that the percentage of improvement for male and female was 12.16% and 2.7% in the URB arm compared to that in the LAA arm (9.9% and 2.5%).

Figure 5 shows the percentage of improvement within the age categories for children. Overall, children in 3–5 years age category showed the rate of improvement of 7.1% compared to children in 6–7 years and 8–9 years age categories with the rates of 5.16% and 1.29%, respectively. A breakdown of the results by trial arms showed that the rate of improvement for children in 3–5 years category is 7.41% in the LAA arm compared to a rate of 6.76% in the URB arm. This observation is reversed in the 8–9 years categories, where 1.35% improvement was recorded for URB arm and 1.23% improvement in LAA arm.

Figure 6 shows the percentage of improvement by ethnic group. This indicated that children that identified as white had the rate of improvement of 9.03% versus 4.52% for non-white.

Primary analysis represented by risk difference

	LAA	URB	URB – LAA	
CGI-I	*n*/*N* (%)	*n*/*N* (%)	Risk difference (95% CI)	*p*-value
Improved	10/81 (12.35%)	11/74 (14.86%)	0.03 (−0.10 to 0.14)	0.51
Not improved	71/81 (87.65%)	63/74 (85.14%)		

We have represented the results of the primary analysis in terms of risk difference. The estimated difference of improvement proportion between arms in the favour of URB was 0.03 with 95% CI of −0.10 to 0.14. The standard errors were estimated using bootstrap approach.

CGI-I on its original scale

CGI-I is a 7-point scale measure (1 – very much improved; 2 – much improved; 3 – minimally improved; 4 – no change; 5 – minimally worse; 6 – much worse; or 7 – very much worse). The motivation here is to compare the improvement between trial arms based on CGI-I original scale.

TABLE 26 Summary of analysis on CGI-I on its original scale

	LAA	URB	Total	URB vs. LAA
Variable	***n/N* (%)**	***n/N* (%)**	***n/N* (%)**	**Odds ratio (95% CI)**
Not assessed	0/81 (0%)	0/74 (0%)	0/155 (0%)	0.88 (0.49 to 1.57)
Very much improved	0/81 (0%)	2/74 (2.7%)	2/155 (1.29%)	
Much improved	10/81 (12.35%)	9/74 (12.16%)	19/155 (12.26%)	
Minimally improved	20/81 (24.69%)	20/74 (27.03%)	40/155 (25.81%)	
No change	29/81 (35.8%)	23/74 (31.08%)	52/155 (33.55%)	
Minimally worse	20/81 (24.69%)	17/74 (22.97%)	37/155 (23.87%)	
Much worse	2/81 (2.47%)	3/74 (4.05%)	5/155 (3.23%)	
Very much worse	0/81 (0%)	0/74 (0%)	0/155 (0%)	
Missing	32/113 (28.32%)	40/114 (35.09%)	72/227 (31.72%)	

Table 26 indicated that for the participants in the LAA arm the odds of having a better rank in improvement was 12% lower compared to URB; however, it is not significant (OR 0.88, 95% CI 0.49 to 1.57) which was consistent with primary analysis result.

Appendix 4 Coronavirus disease 2019 impact

Families were participants on the trial for a considerable length of time from baseline to 52 weeks follow-up. With the onset of COVID-19 and associated restrictions and adjustments to the trial delivery (see COVID-19 chapter for a comprehensive description of the impact of COVID-19 on trial procedures), it is important to try to ascertain what, if any, impact COVID-19 may have had on study delivery and outcomes. A minority of families (n = 47) completed their participation in the trial up to the 24-week follow-up assessment prior to March 2020 and therefore experienced the trial in its original format. For all other families, a combination of pre-COVID-19 trial arrangements and during the pandemic restrictions were in place. For example, some families may have had baseline assessment pre COVID and all other procedures (intervention and follow-up assessments) post March 2020, while others had baseline assessment and intervention pre-COVID and 24-week follow-up post March 2020 and some had all study procedures after March 2020 during COVID-19 restrictions. This makes it challenging to allocate participants to subgroups to determine any putative impact of COVID-19 on study outcomes. For this study we decided to define those participants who received their 24-week follow-up assessments before 23 March 2020 as the pre-lockdown group and all other participants as the post-lockdown group. Of course, virtually all participants had their 52-week follow-up assessments during the COVID-19 pandemic. While it is acknowledged that this results in uneven numbers on the two groups, it enables us to be confident that those in the pre-lockdown group completed baseline, intervention and primary outcomes before the start of the COVID-19 pandemic.

Table 27 shows that the majority of the 24-week assessment visits were post lockdown in both arms.

From *Table 28*, among participants treated in URB arm compared with those in the LAA arm, the odds of improvement post lockdown (23 March 2020) on average was 73% higher compared to the pre-lockdown period. However, the CI was very wide and included differences that favoured either group (OR 1.73, 95% CI 0.36 to 8.27; p = 0.49).

To see visually whether COVID-19 introduces any interruption in the trend between the probability of improvement according to primary outcome and time in pre and post lockdown and to see whether there is any discontinuity gap between the two groups, a baseline linear trend model is used in *Figure 7* to account for differences in pre- and

TABLE 27 Visit 24 weeks and lockdown cut-off date

	LAA	URB	Total
Variable	***n/N* (%)**	***n/N* (%)**	***n/N* (%)**
Pre lockdown	26/81 (32%)	21/75 (28%)	47/156 (30%)
Post lockdown	55/81 (68%)	54/75 (72%)	109/156 (70%)

TABLE 28 Coronavirus disease 2019 impact on the primary outcome

	LAA	URB	URB vs. LAA compared to pre-lockdown	
Variable	***n/N* (%)**	***n/N* (%)**	**Odds ratio (95% CI)**	***p*-value[a]**
CGI-I				
Improved pre lockdown	5/26 (19.23%)	4/20 (20%)	1.73 (0.36 to 8.27)	0.49
Improved post lockdown	5/55 (9.09%)	7/54 (12.96%)		

a *p*-value obtained from GEE with binomial distribution.

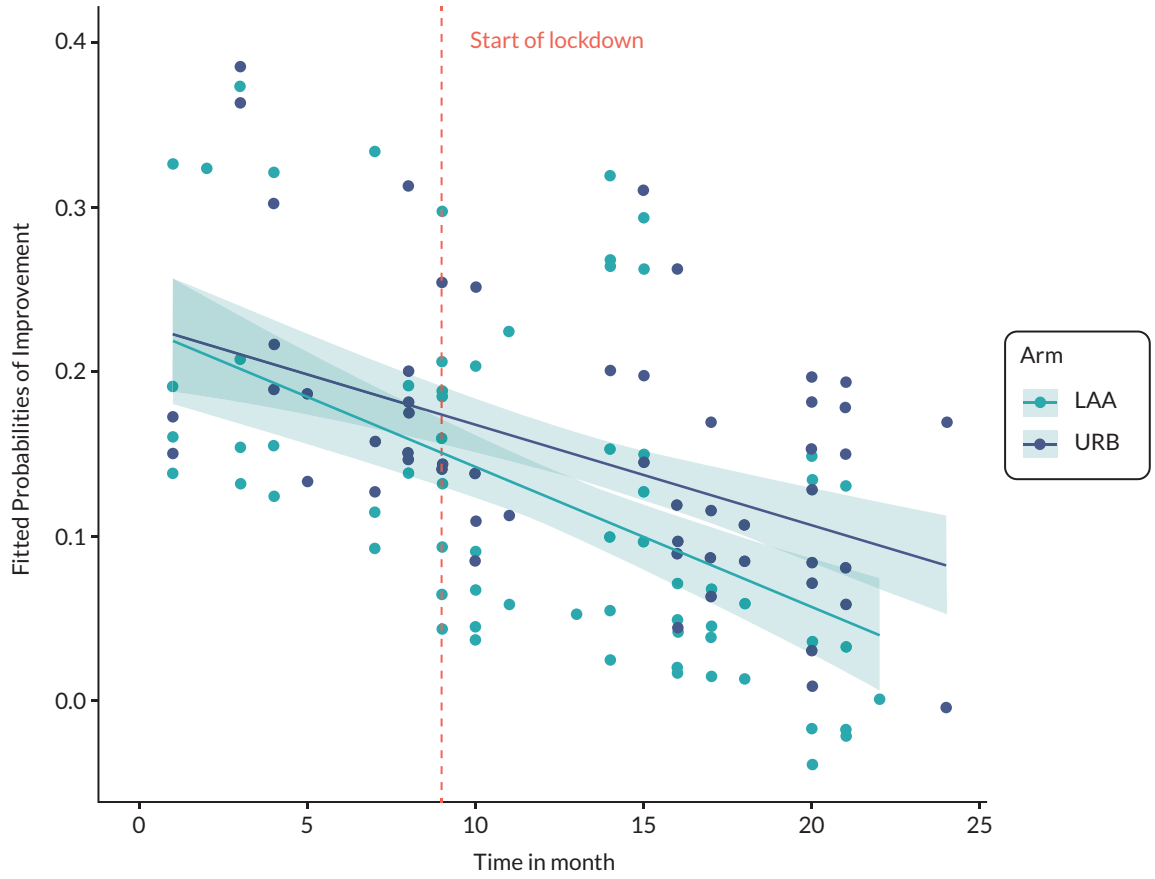

FIGURE 17 The linear trend between fitted probabilities of improvement vs. time in month pre and post lockdown.

TABLE 29 Event of special interest summary pre and post lockdown

Variable	Total *n*/*N* (%)
Pre lockdown	13/24 (54%)
Post lockdown	11/24 (46%)

post-lockdown trends by including a linear term for time in month. The fitted values of probabilities of improvement were plotted versus the time in month.

Figure 17 shows the linear trend of fitted probabilities of improvement pre and post lockdown (vertical dashed line) per trial arms. As expected from the COVID-19 impact analysis, there was no discernible jump in the trend or discontinuity gap pre and post lockdown. Therefore, it was not expected that the probability of improvement differs between these two period in each trial arm.

Table 29 shows that the ESIs are almost equally distributed pre and post lockdown.

Appendix 5 Summary of health economic costs

TABLE 30 Summary of the intervention costs

Intervention costs in the URB and LAA groups								
	Source							
Type of cost	URB				LAA			
Staff	*Unit*	*Frequency*	*Source*	*Cost (£)*	*Unit*	*Frequency*	*Source*	*Cost (£)*
	Band 5 – clinical assistant	32 hours	PSSRU	£1152.00	NAS Staff Member	180 hours	NAS 2021	£1440.00
	Band 7 – clinical psychologist	32 hours	PSSRU	£1856.00	NAS Staff Member	50 hours	NAS 2021	£1500.00
Printed materials		9 units	Assumption	£90.00		9 units	NAS	£90.00
Total (per participant in group of nine)				£344.22				£336.67

TABLE 31 Summary of time, travel and out-of-pocket costs in each arm

	URB group	LAA group
Treatment	Mean £ (SD)	Mean £ (SD)
Travel costs	21 (35)	15 (22)
Time costs	130 (226)	95 (198)
Private out-of-pocket costs	113 (553)	132 (923)

TABLE 32 Summary of time costs for time spent off school

	URB group (*n* = 106)	LAA group (*n* = 104)
Treatment	Mean £ (SD)	Mean £ (SD)
Time spent off school	497 (573)	471 (573)

TABLE 33 Summary of inpatient and day-case costs in each arm

	URB group			LAA group		
	Mean £ (SD)			Mean £ (SD)		
Treatment	24 weeks	52 weeks	Mean	24 weeks	52 weeks	Mean
Inpatient stays	32 (139)	20 (138)	51 (256)	14 (95)	75 (590)	101 (642)
Day cases	69 (266)	99 (379)	185 (584)	21 (128)	81 (356)	70 (331)

TABLE 34 Unit costs for hospital stays

Item	£	Unit	Reference	Notes
Inpatient	378	Per night	National reference costs 2019/2020 v2	Ward costs per day
Day-case cost	812	Per day case	National reference costs 2019/2020 v2	Per day-case unit cost

TABLE 35 Appointment and drug costs in each arm at baseline

NHS healthcare costs in the URB and LAA groups		
	URB group	LAA group
	Appointments	
	Mean £ (SD)	Mean £ (SD)
Cost category	Baseline	Baseline
GP	44 (66)	54 (137)
GP out of hours	8 (28)	19 (68)
Community nurse	8 (58)	3 (10)
Community support worker	2 (13)	4 (19)
Social worker	14 (57)	9 (34)
CAMHS	74 (215)	116 (285)
School nurse	126 (840)	83 (646)
Counsellor	18 (135)	31 (240)
NHS 24/NHS 111 phone line	1 (3)	2 (6)
Psychiatrist	28 (108)	11 (61)
Psychologist	118 (440)	46 (101)
Occupational therapist	93 (389)	276 (1038)
Paediatrician	316 (445)	306 (307)
Speech and language therapist	265 (566)	349 (659)
Accident and emergency	23 (64)	18 (52)
Other consultations		
Other	34 (172)	53 (294)
Medications		
Atomoxetine	0 (0)	3 (21)
Mirtazapine	0 (1)	0 (0)
Propranolol	0 (1)	0 (0)
Sertraline	0 (1)	0 (0)
Fluoxetine	0 (1)	0 (0)
Other medications		
Other	48 (161)	66 (146)

TABLE 36 Unit costs for appointments

Appointments	Unit cost (£)	Source	Comments
GP – in practice	39.23	PSSRU 2020	Cost per patient contact
GP – by phone	15.32	PSSRU 2020	GP led triage phone appt
GP – at home	156.00	PSSRU 2020	Based on an hour of General Medical Services
GP – out of hours	75.74	Department of Health and NHS England[76]	Based on 2014 values updated to 2020 value.
Community nurse – in practice	12.67	PSSRU 2020	Based on assumption of 20 min appointment
Community nurse – by phone	7.62	PSSRU 2020	Nurse-led triage phone appt
Community nurse – at home	43.44	National reference costs 2019/2020 v2	District nurse, adult, face to face
Community support worker	25.00	PSSRU 2020	Per hour of community support worker time
Social worker	46.00	PSSRU 2020	Per hour, social worker (children's)
CAMHS	288.00	PSSRU 2020	Child and Adolescent Mental Health Services, outpatient attendance
School Nurse	54.00	PSSRU 2020	School-based children's health care (other) services – group single professional (one to one)
Counsellor	97.00	PSSRU 2020	Per hour, based on an assumption of an hour's appointment.
NHS 111 phone line	9.19	Turner *et al.*[77]	Based on estimate of £8 (2012) adjusted for 2020 costs
Psychiatrist	361.00	National reference costs 2019/2020 v2	Child and adolescent psychiatry, unit costs
Psychologist	201.00	National reference costs 2019/2020 v2	Clinical psychology, unit cost
Occupational therapist – in practice	155.00	National reference costs 2019/2020 v2	Unit cost, child one to one.
Occupational therapist – at home	141.00	PSSRU	Community services – occupational therapy
Paediatrician	351.00	National reference costs 2019/2020 v2	Paediatric neuro-disability
Speech and language therapist	112.00	National reference costs 2019/2020 v2	Speech and language therapist, child, one to one
Accident and emergency	113.00	National reference costs 2019/2020 v2	Accident and emergency unit cost

TABLE 37 Unit costs for medications

Medication	Dose (mg)	Administration	Pack cost (£)	Dose cost (£)	Source	Comments
Atomoxetine	10	Capsule	21.34	0.76	BNFC Online 2022[78]	28 capsules – tariff price
	18	Capsule	21.34	0.76	BNFC Online 2022[79]	28 capsules – tariff price
	40	Capsule	23.52	0.84	BNFC Online 2022[78]	28 capsules – tariff price
Mirtazapine	15	Capsule	1.50	0.05	BNFC Online 2022[78]	28 capsules – tariff price
Propranolol	10	Capsule	1.54	0.06	BNFC Online 2022[78]	28 capsules – tariff price
Sertraline	50	Capsule	1.94	0.07	BNFC Online 2022[78]	28 capsules – tariff price
Fluoxetine	20	Capsule	0.83	0.03	BNFC Online 2022[80]	30 capsules – tariff price

BNFC, British National Formulary for Children.

TABLE 38 Unit costs for private therapies

Private costs for appointments			
Appointments	**Unit cost (£)**	**Source**	**Comments**
Homeopathy	93.94	Trichard *et al.*[81]	Estimate taken from a study managing children with recurrent acute rhinopharyngitis managed by homeopathy. Revised to be more reflective of GBP 2020 costs
Traditional Chinese medicine	23.00	University of Westminster[82]	Assumption based on provider estimates
Private counselling	45.00	Bark[83]	Assumption based on provider estimates
Private occupational therapy	43.63	Royal College of Occupational Therapists[84]	Cost £42 per session, published 2018 adjusted to 2020[85]
Private speech and language therapy	70.00		Assumption based on a number of provider estimates
Mindfulness	45.00		Assumed to be the same value as counselling
Aromatherapy	50.00	Aromatherapy Council[86]	Assumption based on provider estimates

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